FORMULATION, *IN-VITRO* AND *EX-VIVO* EVALUATION OF NON-EFFERVESCENT FLOATING MICROPARTICULATES OF CELECOXIB

Dissertation Submitted to

The Tamil Nadu Dr. M.G.R. Medical University,

Chennai - 600 032

In partial fulfillment for the award of Degree of

MASTER OF PHARMACY

(Pharmaceutics)

Submitted by

SUJITHA. M

Register No. 26116013

Under the Guidance of

Prof. K. SUNDARAMOORTHY, B.Sc., M. Pharm.,

Department of Pharmaceutics

ADHIPARASAKTHI COLLEGE OF PHARMACY

Accredited By "NAAC" with a CGPA of 2.74 on a Four point Scale at B Grade

MELMARUVATHUR - 603 319

APRIL - 2013

CERTIFICATE

This is to certify that the research work entitled **"FORMULATION, *IN-VITRO* AND *EX-VIVO* EVALUATION OF NON-EFFERVESCENT FLOATING MICROPARTICULATES OF CELECOXIB"** submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfillment for the award of the Degree of the Master of Pharmacy (Pharmaceutics) was carried out by **SUJITHA. M (Register No. 26116013)** in the Department of Pharmaceutics under my direct guidance and supervision during the academic year 2012-2013.

Place: Melmaruvathur

Date:

Prof. K. SUNDARAMOORTHY, B.Sc., M.Pharm.,
Department of Pharmaceutics,
Adhiparasakthi College of Pharmacy,
Melmaruvathur - 603 319,
Tamil Nadu.

CERTIFICATE

This is to certify that the dissertation entitled **"FORMULATION, *IN-VITRO* AND *EX-VIVO* EVALUATION OF NON-EFFERVESCENT FLOATING MICROPARTICULATES OF CELECOXIB"** the bonafide research work carried out by **SUJITHA.M (Register No. 26116013)** in the Department of Pharmaceutics, Adhiparasakthi College of Pharmacy, Melmaruvathur which is affiliated to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, under the guidance of **Prof. K. SUNDARAMOORTHY, B.Sc., M.Pharm., Department of Pharmaceutics, Adhiparasakthi College of Pharmacy,** during the academic year 2012-2013.

Place: Melmaruvathur

Date:

Prof. (Dr.) T. VETRICHELVAN, M.Pharm., Ph.D.,
Principal,
Adhiparasakthi College of Pharmacy,
Melmaruvathur - 603 319,
Tamil Nadu.

ACKNOWLEDGEMENT

First and foremost, I wish to express my deep sense of gratitude to his Holiness **ARULTHIRU AMMA,** President, ACMEC Trust, Melmaruvathur for his ever growing Blessings in each step of the study.

With great respect and honor, I extend my thanks to our Vice president **THIRUMATHI LAKSHMI BANGARU ADIGALAR,** ACMEC trust, Melmaruvathur, for her excellence in providing skillful and compassionate spirit of unstinted support to our department for carrying out research work entitled **"FORMULATION, *IN-VITRO* AND *EX-VIVO* EVALUATION OF NON-EFFERVESCENT FLOATING MICROPARTICULATES OF CELECOXIB".**

I concede my in most special gratitude and thanks to **Prof. K. SUNDARAMOORTHY, B.Sc., M.Pharm.**, Professor, Department of Pharmaceutics, Adhiparasakthi College of Pharmacy, for the active guidance, innovative ideas, creative works, infinite helps, indulgent and enthusiastic guidance, valuable suggestions, a source of inspiration where the real treasure of my work.

I express my cordial thanks to **Prof. (Dr.) T.VETRICHELVAN, M.Pharm., Ph.D.,** Principal, Adhiparasakthi College of Pharmacy, without his encouragement and supervision it would have been absolutely impossible to bring out the work in this manner.

In this opportunity to express my sincere thanks to **Dr. S. SHANMUGAM, M.Pharm., Ph.D.,** Professor, **Mr. T. AYYAPPAN, M.Pharm.,** Assistant Professor, **Mr. A. UMAR FARUKSHA, M.Pharm.,** Assistant Professor, Department of Pharmaceutics, **Mr. K. ANANDHA KUMAR, M.Pharm.,** Assistant Professor**,**

Department of pharmaceutical analysis, **Mrs. (Dr.) D. NAGAVALLI, M.Pharm., Ph.D.,** Professor, Department of pharmaceutical chemistry, for encouragement and support for the successful completion of this work.

My special thanks to our lab technicians **Mrs. S. KARPAGAVALLI, D.Pharm., B.B.A.,** and **Mr. M. GOMATHI SHANKAR, D.Pharm.,** for their kind help throughout this work.

I am indeed very much thankful to the librarian **Mr. M. SURESH, M.L.I.S.,** for providing all reference books for the completion of this project.

My special thanks to **Mr. S. MURUGANANTHAM, M.Pharm.,** Manager - Production, Axon Drugs Pvt Ltd., **Mr. K. VINAYAGAMOORTHY, M.Sc.,** Sr. Manager – Quality Control, Actavis., and **Mr. KARUPPIAH VELLAIAN, M.Pharm, MBA,** Director – IPDO, Dr. Reddy's Laboratories, for providing free sample of drug and helping in analysis of samples.

I am thankful to all my class FRIENDS and SENIORS for their support and suggestion during my work.

Finally yet importantly, I gratefully forward my affectionate thanks to my FAMILY MEMBERS and my BELOVED ONES for their frequent prayers, which has sustained me a lot in the successful completion of my project work**.**

SUJITHA. M.

My heartfelt dedication to my beloved Parents and my beloved ones…

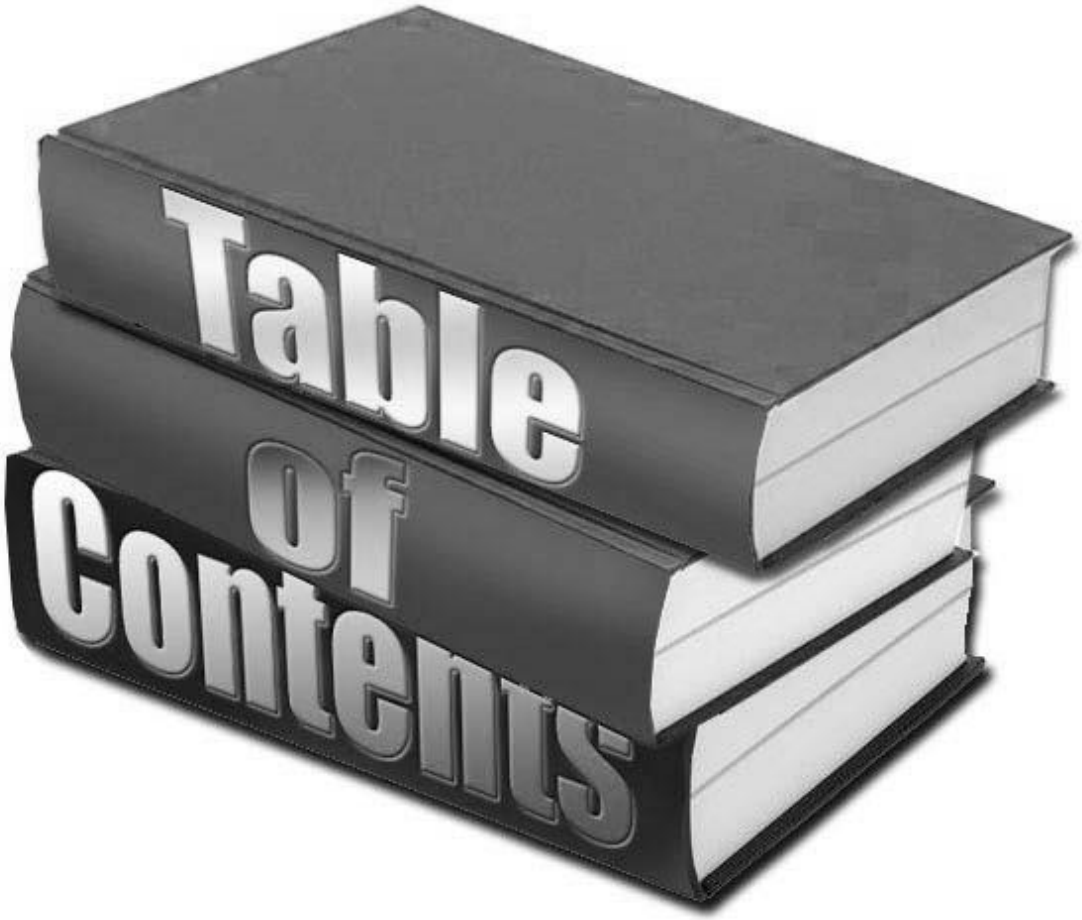
Table
of
Contents

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS USED

λ max	Absorption maximum
ºC	Degree Celsius
<	Less than
>	More than
µm	Micro meter
µg	Micro gram
±	plus or minus
%	Percentage
θ	theta
ADME	Absorption, Distribution, Metabolism and Excretion
API	Active Pharmaceutical Ingredient
approx	Approximately
AUC	Area under curve
BA	Bioavailability
BCS	Biopharmaceutics Classification System
BP	British Pharmacopeia
CAS	Chemical Abstracts Service
cm	Centimeter

cP	Centipoise
COX	Cyclooxygenase
CR	Controlled Release
CRDDS	Controlled Release Drug Delivery System
DCP	Dicalcium phosphate
DMSO	Dimethyl Sulfoxide
DSC	Differential Scanning Calorimetry
ER	Extended Release
FDDS	Floating Drug Delivery System
FTIR	Fourier Transform Infra Red
GET	Gastric Emptying Time
GI	Gastro intestinal
GIT	Gastro intestinal tract
gm / gms	Gram / Grams
GRDF	Gastro Retentive Dosage Forms
GRT	Gastric Residence Time
h / hr / hrs	Hour / Hours
HBS	Hydrodynamically Balanced Systems
HCl	Hydrochloric acid

HPMC	Hydroxy Propyl Methyl Cellulose
i.e	that is
ICH	International Conference on Harmonization
IP	Indian Pharmacopeia
IVIVC	*In-vitro in-vivo* correlation
JP	Japanese Pharmacopeia
KBr	Potassium Bromide
KPSI	Kilo Pounds per square inch
L	Liter
LOD	Loss on drying
m^2	Square Meter
MA	Micro Ampere
max	Maximum
MCC	Microcrystalline cellulose
mcg	Microgram
mg	Milligram
min	Minute
ml / mL	Milliliter
mm	Millimeter

MMC	Migrating Myoelectric Cycle
mPas	Milli Pascal seconds
N	Normality
NA	Not applicable
NaOH	Sodium Hydroxide
NF	National Formulary
nm	Nano meter
No.	Number
NP	Nano particles
NSAID	Non Steroidal Anti-Inflammatory Drug
PCL	Poly-capro lactone
PDI	Poly Dispersity Index
PEG	Polyethylene glycol
PG	Prostaglandin
pH	Potential of Hydrogen
Ph Eur	European Pharmacopoeia
pKa	Negative logarathim of acid dissociation constant
PLA	Poly-lactide
PVD	Physical Vapor Deposition

RH	Relative Humidity
rpm	Revolutions per minute
RSM	Response Surface Methodology
s	Seconds
S.D	Standard Deviation
S.No.	Serial Number
SEM	Scanning Electron Microscope
SGF	Simulated Gastric Fluid
SLS	Sodium Lauryl Sulphate
SR	Sustained Release
USFDA	United States Food and Drug Administration
USP	United States Pharmacopeia
UV	Ultra Violet
Vs	versus
w/v	Weight by Volume
w/w	Weight by Weight

INTRODUCTION

1. INTRODUCTION

1.1. NOVEL DRUG DELIVERY SYSTEM *(Bankar G.S and Rhodes C.T., 2009; Brahmankar D.M and Jaiswal S.B., 1995; Chein Y.W., 1995)*

The goal of a sustained release dosage form is to maintain therapeutic blood or tissue levels of the drug for an extended and specified period of time. This is generally accomplished by attempting to obtain "zero-order" release from the dosage form. Zero-order release constitutes drug release from the dosage form which is independent of the amount of drug in the delivery system (i.e. a constant release rate). Sustained-release systems generally do not attain this type of release and usually try to mimic zero-order release by providing drug in a slow first-order fashion (i.e., concentration release dependent). Systems that are designated as prolonged release can also be considered as attempts at achieving sustained-release delivery.

The term "Controlled- release drug product" has been used to describe various types of oral extended release rate dosage forms, including sustained release (SR), sustained action, prolonged action, long action and retarded release. These terms for extended release dosage forms were introduced by drug companies to reflect a special design for producing an extended release (ER) dosage form or used as a marketing term.

In the last two-three decades interest in sustained release drug delivery systems is remarkably increasing. This has been due to various factors viz.

- Developing new drug entities.
- Expiration of international patents.
- Discovery of new polymeric materials suitable for prolonging the drug release.

- Need of therapeutic efficacy and safety achieved by sustained release drug delivery.

The subject of sustain release has been reviewed by various authors. Several books have been published on it. These reviews and books provide not only the mechanisms and technology of production of dosage forms but also the information on clinical evidence and performance.

There are many definitions of sustained release but the simplest definition is "Any drug or dosage form or medication that prolongs the therapeutic activity of drug''. The overall objective is that, once the drug-carrier material has been injected or otherwise implanted or taken orally into the body, the drug is released at a predetermined rate for some desired period of time. Controlled release technology is relatively new field and as a consequence, research in this field has been extremely fertile and has produced many discoveries.

Non-immediate release delivery systems may be divided conveniently into 4 categories,

A. Delayed release

B. Sustained release

a) Controlled release

b) Prolonged release

C. Site- specific release

D. Receptor release

Delayed – release systems are those that use repetitive, intermittence dosing of a drug from one or more immediate release units incorporated into a single dosage forms to make delayed action. Example: Repeat- action tablets and capsules, enteric coated tablets where timed release achieved by a barrier coating.

Sustained- release systems includes any drug delivery system that achieves slow release of drug over an extended period of time.

Controlled release systems are those systems which are successful maintaining constant drug levels in blood or target release (i.e.) release rate of drug occurs in controlled manner.

Prolonged released systems only extends the duration of action and drug release that achieved by conventional drug delivery.

Site specific and receptor release refers to targeting of drug directly to a certain biological location. In the case of site- specific release, the target is a certain organ or tissue, for receptor release, the target is the particular receptor for a drug within an organ or tissue.

Control release system differs from Sustain release system which simply prolongs the drug release and hence plasma drug levels for an extended period of time (i.e. not necessarily at a predetermined rate). Thus the chief objective of most products should be controlled delivery to reduce dosing frequency to an extent that once daily dose is sufficient for therapeutic management through a uniform plasma concentration at steady state.

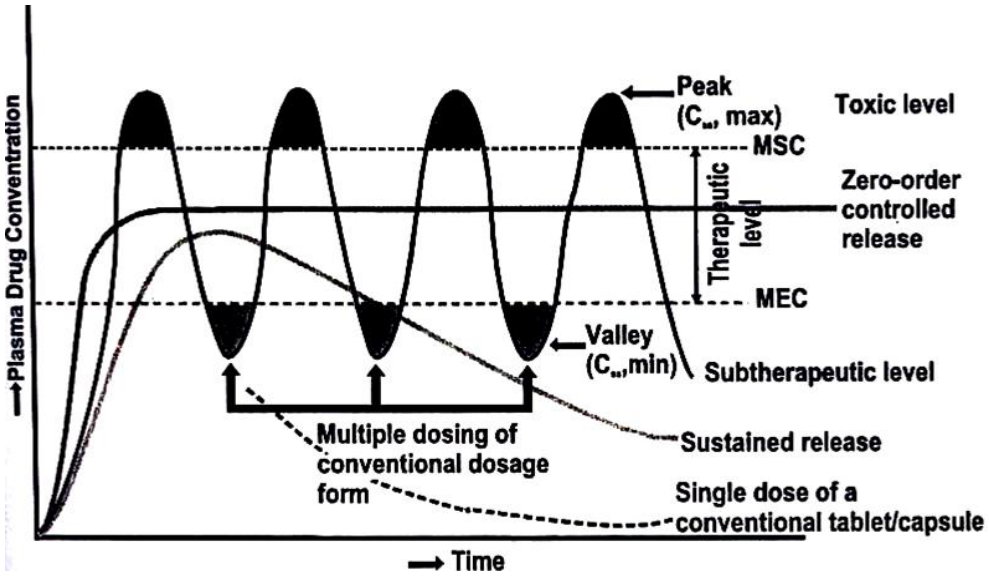

Figure 1.1 A hypothetical plasma concentration Vs time profile from conventional multiple and single doses of sustained release drug delivery formulations.

1.2 ANATOMY AND PHYSIOLOGY OF STOMACH *(Tortora G. and Derrickson B., 2003; Ramesh R.P. and Mahesh C.P.,2009; Aulton M.E., 2002)*

Stomach is an organ with capacity for storage and mixing. It is located just below the diaphragm in the epigastric and left hydrochondriac region of the abdomen.

The stomach is anatomically divided into three parts:

- Fundus
- Body
- Pylorus (Antrum)

Stomach is made up of fundus and body regions. They are capable of displaying a large expansion to accommodate food without much increase in intragastric pressure.

Stomach lining is devoid of villi and it consists of considerable number of gastric pits that contribute to storage capacity of the stomach. Ant rum region is responsible for the mixing and grinding of gastric content. There are two main secretions: mucus and acid, produced by specialized cell in stomach lining. Mucus is secreted by goblet cells and gastric acid by parietal cells (oxyntric) The Mucus spread and cover the rest of GI tract. Under fasting condition the stomach is a collapsed bag with a residual volume of 50 ml and contains a small amount of gastric fluid (pH 1-3) and air.

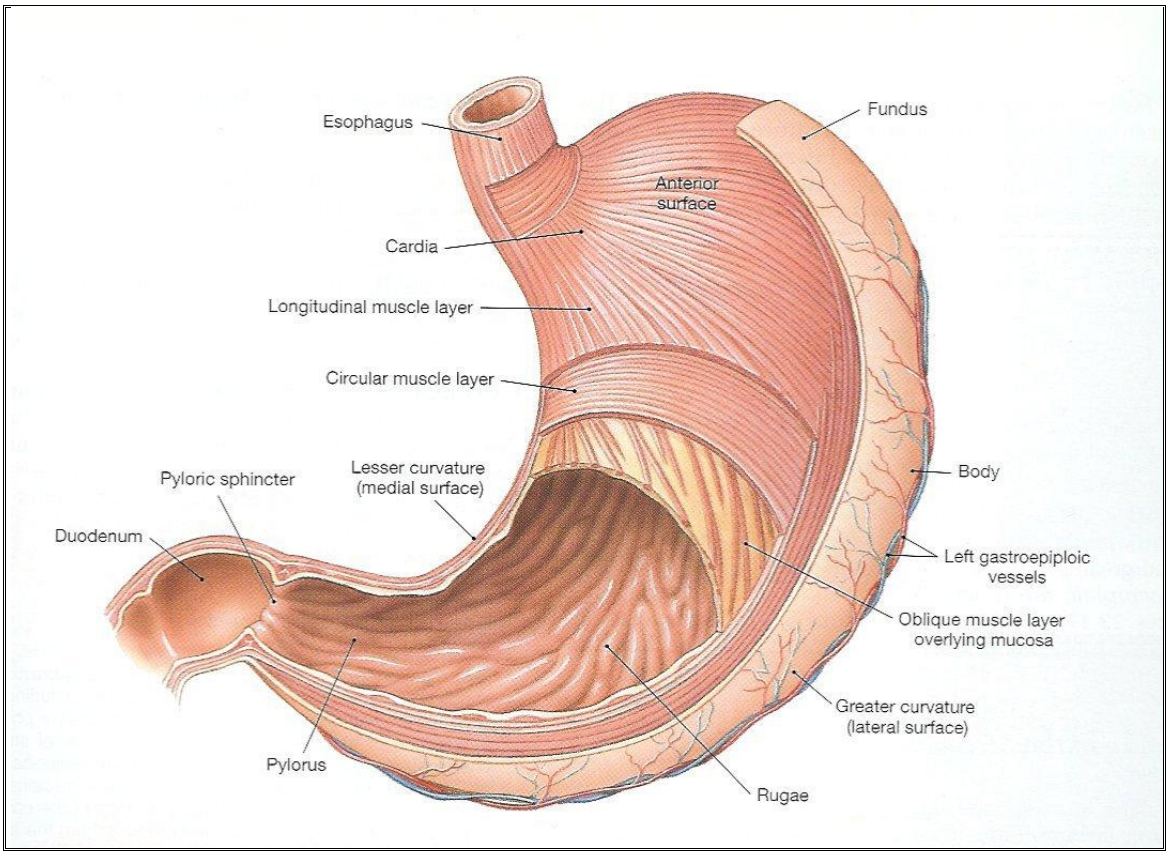

Figure 1.2 Structure of Stomach

- **Physiology:**

The physiology and disease state of stomach has a direct effect on design of controlled drug delivery system because drug is absorbed from and enters into site of

action. Factors such as pH, nature and volume of gastric secretions and gastric mucosa play an important role in drug release and absorption.

- **pH:**

Environmental pH affects the performance of orally administered drugs. The pH of stomach in fasted condition is about 1.5 to 2 and in fed conditions it is usually 2 to 6. A large volume of water administered with oral dosage form changes the pH of stomach to pH of water initially. This change occurs because stomach does not have enough time to produce sufficient quantity of acid before emptying of liquid from the stomach.

Table 1.1 Anatomical difference between different regions of the GIT

Particulars	Stomach	Small intestine	Large intestine	Rectum
pH range	1-3	5-7.5	7.9-8.0	7.5-8.0
Length (cm)	20	285	110	20
Diameter (cm)	15	2.5	5	2.5
Surface area (m^2)	0.1-0.2	200	0.15	0.02
Blood flow (L/min)	0.15	1.0	0.02	-
Transit time (hrs)	1-5	3-6	6-12	6-12

- **Volume:**

The resting volume of stomach is about 25-52 ml. Gastric volume is important for dissolution of the dosage forms *in-vivo*. Meyer et al. conducted an experiment to study the effect of gastric fluid volume on absorption of controlled release theophylline dosage form in human beings. During this experiment they measured the gastric fluid volume of each subject. They estimated the mean gastric fluid volume in normal and achlorhydric subjects. The mean volume recovered by gastric aspiration over three consecutive, 15 min. time periods was 61+51 ml in achlorhydric subjects and 98+38 ml in normal subjects. Thus, there is such a large volume difference in gastric secretions that would significantly affect *in-vivo* dissolution of drugs.

- **Gastric mucosa:**

Simple columnar epithelial cells line the entire mucosal surface of the stomach. Mucus, parietal and peptic cells are present in the body of stomach. These cells are associated with different functions. The parietal cells secrete acid whereas the peptic cells secrete precursor for pepsin. The surface mucosal cells secrete the mucus and bicarbonate. They protect the stomach from digestion by pepsin and from the adverse effects of hydrochloric acid. As mucus has lubricating effect, it allows chyme to move freely through the digestive system.

- **Gastric secretion:**

Acids, pepsin, gastrin, mucus and some other enzymes are the secretions of the stomach. Normal adults produce a basal secretion up to 60 ml with approximately 4 milli

mol of hydrogen ions every hour. Other potent stimulators of gastric acid are the hormones like gastrin, peptides, amino acids and gastric distention.

- **Liquid in fasted and fed conditions**:

Volumes of liquids affect gastric emptying of liquids, larger the volume, faster the emptying. Gastric emptying of small volumes like 100 ml or less is governed by the MMC cycle whereas large volumes of liquids 200 ml or more are emptied out immediately after administration.

- **Effect of food on gastric secretion:**

Type of meal and its caloric content, volume, viscosity and co-administered drugs affect gastric secretions and gastric emptying time. The rate of emptying primarily depends on caloric contents of the ingested meal. It does not differ for proteins, fats and carbohydrates as long as their caloric contents are the same.

- **Gastric motility:** *(Jain N.K., 2004)*

The pattern series of motility is distinct in fasted and fed states. During the fasting state an inter digestive series of electrical events takes place, which cycle both through stomach and intestine every 2 to 3 hrs. This is called the interdigestive myoelectric cycle or migrating myoelectric cycle (MMC), which is divided into following 4 phases**.**

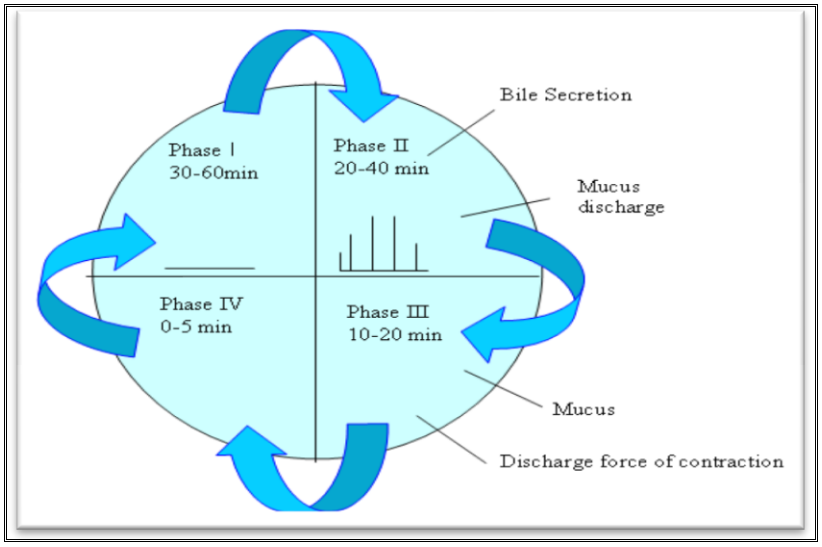

Figure 1.3 Four phases of myoelectric cycle

- Phase I (basal): Lasts for 30 to 60 minutes. Contractions can be characterized by a lack of secretary, electrical, and contractile activity.
- Phase II (preburst): Lasts for 20 to 40 minutes. With intermittent action potential and contractions.
- Phase III (burst): Lasts for 10 to 20 minutes. Includes intense and regular contractions. It is due to this wave that all undigested material is swept out of the stomach down to the small intestine. It is also known as housekeeper wave.
- Phase IV: Lasts for 0 to 5 minutes.

After the ingestion of mixed meal, the pattern of contractions changes from fasted to fed state. It comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (<1 mm), which are propelled toward pylorus. During fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate.

- **Gastric emptying:**

Particle size and feeding state strongly affect the residence time of particles in stomach. Some other factors affecting gastric emptying are as follows:

Type of meal and its caloric content, volume, viscosity and co administered drugs. The rate of gastric emptying primarily depends on the caloric contents of the ingested meal. It does not differ for proteins, fats and carbohydrates as long as their caloric content is the same.

- **Solid In fasted and fed conditions:**

Tablets or capsules do not have any significant calorific value. Therefore, the stomach treats them as an indigestible material. It is known that particle smaller than 2 mm in size are emptied from the stomach quickly. The density of the solid dosage form also affects the gastric emptying time. The average time required for a dosage unit to traverse the GIT is 3–4 hours, although slight variations exist among various dosage forms.

1.3 DRUG PROPERTIES RELEVANT TO SUSTAINED RELEASE FORMULATIONS *(Bankar G.S and Rhodes C.T., 2009; Robinson J.R and Lee V.H.L., 2005)*

During design of sustained release delivery systems, variables such as the route of drug delivery, the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug, are considered of particular interest to the scientist designing the system are the constraints imposed by the properties of the drug.

These properties are classified as,

A) Physicochemical properties

B) Biological properties

These properties have the greatest effect on the behavior of the drug in the delivery system and in the body. There is no clear-cut distinction between these two categories since the biological properties of a drug are a function of its physicochemical properties. By definition, physicochemical properties are those that can be determined from *in-vitro* experiments and biological properties will be those that result from typical pharmacokinetic studies of the absorption, distribution, metabolism, and excretion (ADME) characteristics of a drug and those resulting from pharmacological studies.

A) Physicochemical Properties

a) Dose Size

b) Aqueous Solubility and pKa

c) Partition Coefficient

d) Drug Stability

e) Molecular Size and Diffusivity

f) Drug Protein Binding

B) Biological Properties

a) Absorption

b) Distribution

c) Metabolism

d) Elimination and Biological Half-Life

e) Margin of Safety (Toxicity).

A. Physiochemical properties

a) Dose size: For orally administered drugs, there is an upper limit to the bulk size of the dose to be administered. In general, a single dose of 0.5 – 11.0 gm for conventional dosage form is considered maximal.

b) Aqueous Solubility: Extremes in aqueous solubility are under desirable in the preparation of a SR product. For drug with low water solubility, it will be difficult to incorporate into a SR formulation. The lower limit of solubility for such product has been reported to be 0.1 mg/ml.

c) Partition Co-efficient: Drug that are very lipid soluble or water soluble i.e. extremes in partition co-efficient, will demonstrate either low flux in to the tissues or rapid flux followed by accumulation in the tissues. Both extremes are undesirable for a SR system Eg: Phenothiazines class of compounds is highly lipid soluble.

d) Drug Stability : since most oral SR systems, by necessity are designed to release their contents over much of the length of the GIT, drugs which are unstable in the environment of the intestine might be difficult to formulate into prolonged release systems.

Eg: Propanthdine and Probanthine.

B. Biological properties

a) Absorption: Drugs that are slowly absorbed or absorbed with variable absorption rate are poor candidates for SR systems. For oral dosage forms the lower limit on the absorption rate constant in the range of 0.17 to 0.23 hr^{-1}(assuming GI transit time of 8-12 hr^{-1}).

b) Metabolism: Drugs that are significantly metabolized, especially in region of small intestine, can show decreased bioavailability from SR dosage forms, because less total drug is presented to enzymatic process during a specific period. This allows more complete conversion of drug to its metabolite.

c) Therapeutic Index: Drugs with a narrow therapeutic range which require precise control over the blood levels of the drug are unsuitable for SR dosage forms.

d) Half Life: The biological half life and duration of action of drug obviously plays a major role in considering a drug for SR systems. Drugs with a very short half life (>2 hours) require large amounts of drug to maintain sustained effects and drugs with longer life (<8 hours) because their effects are already sustained.

1.4 GASTRO-RETENTIVE DOSAGE FORM *(Jain N.K., 2004; Garg R. and Gupta G.D., 2008)*

One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), by using gastro-retentive dosage forms (GRDFs). GRDFs can remain in the gastric region for several hours and hence, prolong the gastric residence time of drug. GRDFs offers

several advantages over immediate release dosage form, including the minimization of fluctuations in drug concentration in plasma and at the site of action over prolonged periods of time, resulting in optimized therapeutic efficiencies and reduce the side effect, reduction of total dose administered and reduction of administration frequency, leading to improved patient compliances. Gastro-retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients as compared to the conventional tablet dosage form.

An absorption window exists because of physiological, physicochemical, or biochemical factors. Drugs having site-specific absorption are difficult to design as oral CRDDS because only the drug released in the region preceding and in close vicinity to the absorption window is available for absorption**.**

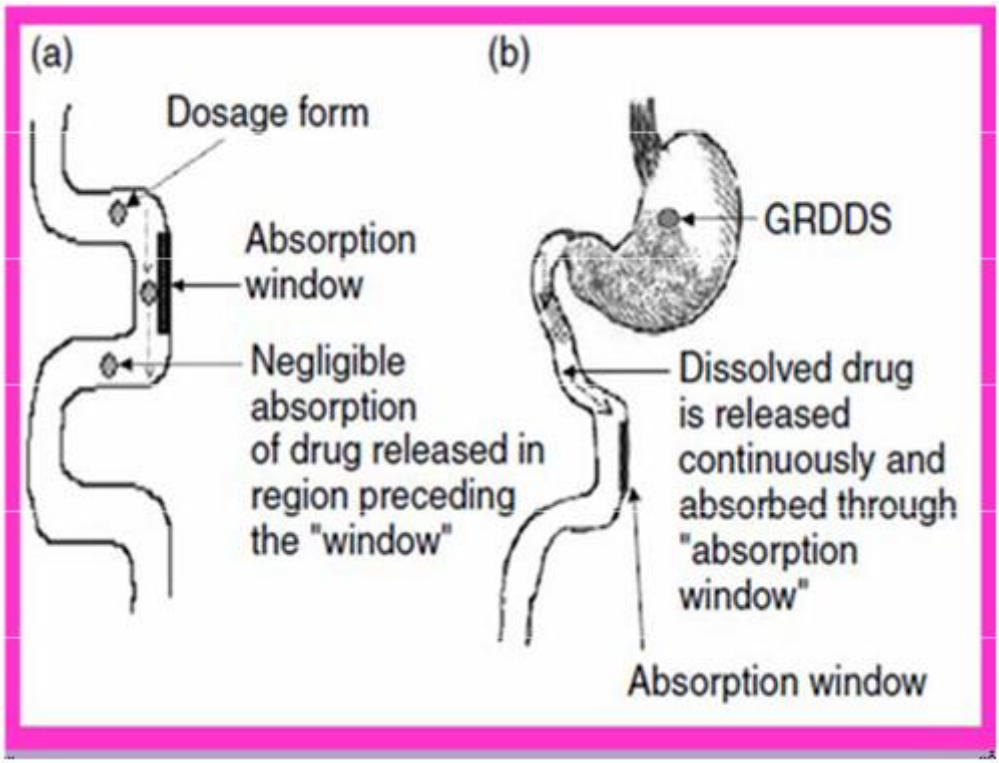

Figure 1.4 Comparison of (a) conventional and (b) gastroretentive drug delivery system

After crossing the absorption window, the released drug goes waste with negligible or no absorption **(Figure 1.4a)**. This phenomenon considerably decreases the time available for drug absorption after its release and expose the success of the delivery system. The GRDDS can improve the controlled delivery of the drugs which exhibit an absorption window by continuously releasing the drug for a prolonged period before it reaches its absorption site, thus ensuring its optimal bioavailability (BA) **(Figure 1.4b)**.

1.5. FACTORS AFFECTING GASTRIC RETENTION *(Anilkumar J.S. and Harinath M.N., 2008; Shweta A. et al., 2005)*

There are several factors that can affect gastric retention of an oral dosage form. These factors are as follows.

- **Density:** The density of a dosage form affects the gastric emptying rate. A buoyant dosage form having a density of less than that of gastric fluids floats. Since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period.
- **Size:** Dosage form units with a diameter of less than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm.
- **Age:** Elderly people, especially those over 70, have a longer GRT.
- **Shape of dosage form:** Ring and tetrahedron shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KPSI) are reported to have better GRT (90% to 100%) of 24 hours compared with other shapes.
- **Single or multiple unit formulation:** Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure

of units, allow co-administration of units with different release profiles or containing incompatible substances. It permits a larger margin of safety against dosage form failure compared with single unit dosage forms.

- **Fed or unfed state:** Under fasting state, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short.
- **Caloric content:** GRT can increase by 4 to 10 hours with a meal that is high in proteins and fats.
- **Nature of meal:** Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state thus, decreasing the gastric emptying rate and prolonging drug release.
- **Frequency of feed:** GRT can increase by over 400 minutes when successive meals are given compare with single meals due to the low frequency of MMC.
- **Gender:** Mean ambulatory GRT in males (3.4 ± 0.6 hours) is less compared with their age and race-matched female counterparts (4.6 ± 1.2 hours), regardless of the weight, height and body surface.
- **Posture**: Gastric emptying is favored while standing and by lying on the right side since the normal curvature of the stomach provides a downhill path whereas, lying on the left side or in supine position, retard it.

- **Disease states:** Diseases like gastro enteritis, gastric ulcer, pyloric stenosis, diabetes and hypothyroidism retard gastric emptying while partial gastrectomy, duodenal ulcer.

1.6. VARIOUS GASTRO-RETENTIVE DRUG DELIVERY SYSTEM *(Sable V. et al.,2010; Mayavanshi A.V. and Gajjar S.S., 2008)*

Various approaches have been pursued to increase the retention of an oral dosage form in the stomach. These include:

A. Bio adhesive delivery system

B. Size increasing system/ Expandable system

C. High density system

D. Floating drug delivery system / Low density system

A. **Bioadhesive system:**

Bio adhesive system is adhering to mucosal surface of the stomach after the oral. This have high turnover rate of gastric mucus and resulting limited retention time. The disadvantage of this system is possibility of oesophageal binding**.**

B. Sized increasing drug delivery system or swelling system:

This dosage forms have initially small size and when enter in the stomach significantly increasing its size above the diameter of the pylorus. The expanded state should be achieved rapidly in order to prevent premature emptying through the pylorus. Conversely, the system should also guarantee their clearance from the stomach after predetermined time intervals to avoid accumulation upon multiple administrations.

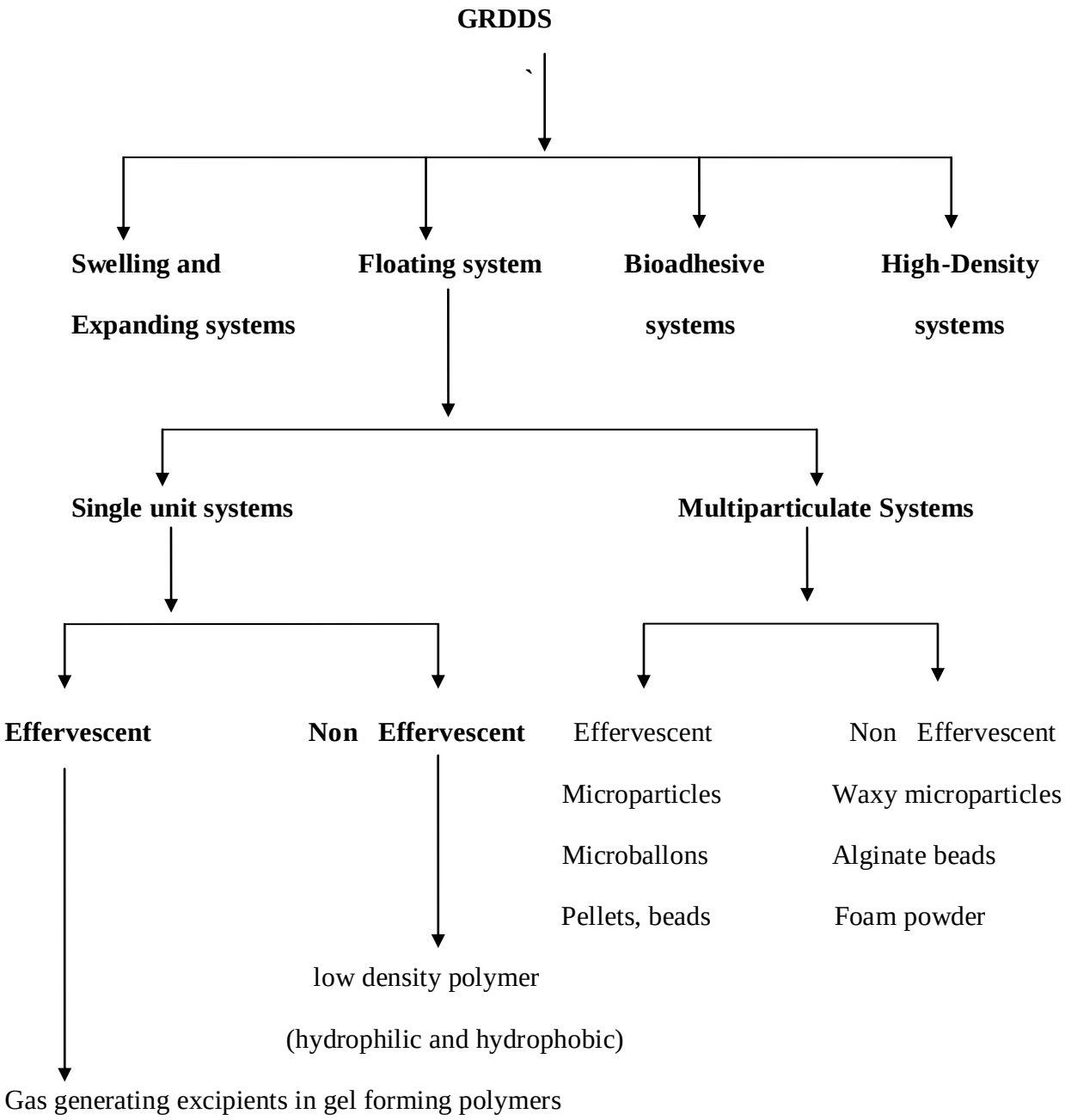

Figure 1.5 Approaches of gastro retentive drug delivery system

C. High-density system:

This system accomplished by coating the drug with a heavy inert material such as barium sulphate, zinc oxide, titanium dioxide, iron powder etc. These coated pellets which have

density greater than that of stomach content (1.004 gm/cm^3). This system having density of ~ 3 gm/cm^3 is retained in the range of the stomach.

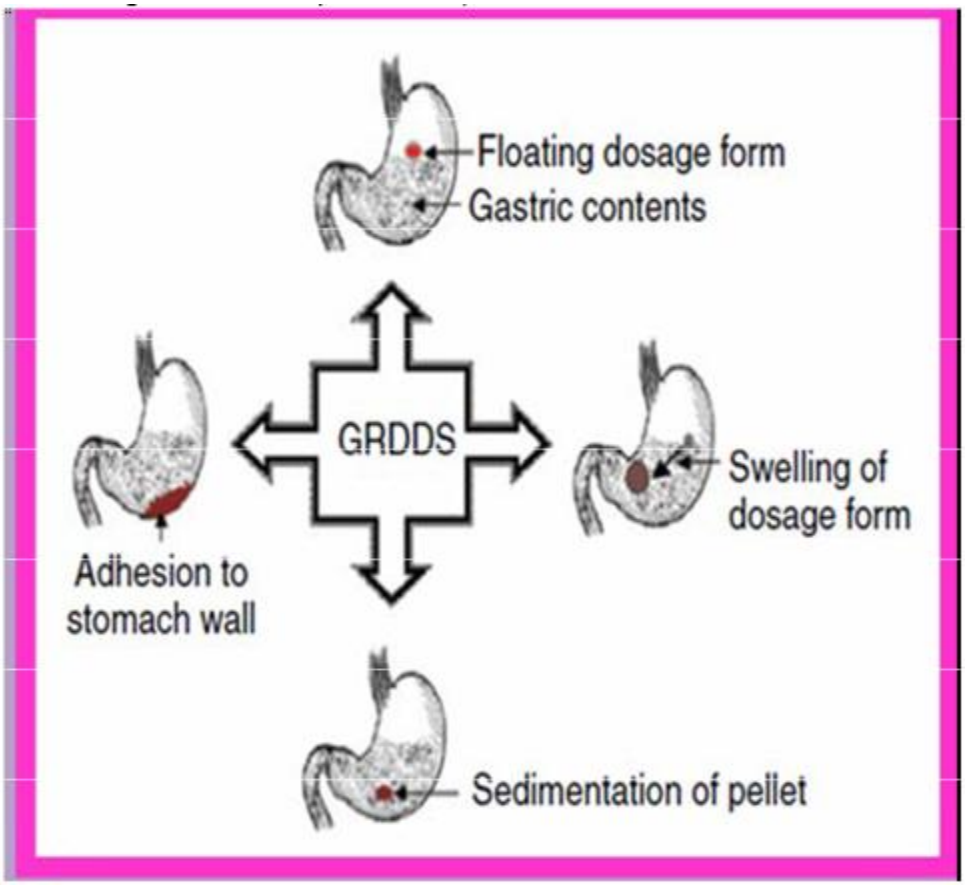

Figure 1.6 Various approaches of gastro retentive drug delivery system

D. Floating drug delivery system:

Floating drug delivery system (FDDS) or hydro dynamically balanced system have a bulk density lower than gastric fluid and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of drug, the residual system is emptied from the stomach. This result in an increase in the GRT and a better control on fluctuation of drug concentration.

1.7 TECHNOLOGICAL DEVELOPMENT IN FDDS *(Bandyopadhyay A.K., 2008; Patil J.M., et al., 2006)*

Based on the mechanism of buoyancy, two distinctly different types, i.e. non-effervescent and effervescent systems have been utilized in the development of FDDS.

A. Effervescent FDDS:

Effervescent system utilize matrices prepared with swellable polymers such as methocel or polysaccharides e.g., chitosan and effervescent components, e.g., sodium bicarbonate and citric or tartaric acid or matrices containing chambers of liquid that gasify at body temperature. The matrices are fabricated so that upon arrival in the stomach, carbon dioxide is liberated by the acidity of the gastric contents and is entrapped in the gellified hydrocolloid. This produces an upward motion of dosage form and maintains its buoyancy.

a. Multiple-unit oral floating drug delivery system:

Recently a multiple–unit type of floating pill, which generates carbon dioxide gas, has been developed. The system consisted of sustained–release pills as seeds surrounded by double layers. The inner layer an effervescent layer containing both sodium bicarbonate and tartaric acid. The outer layer was a swellable membrane layer containing mainly polyvinyl acetate and purified shellac. Moreover, the effervescent layer was divided into two sub layers the sodium bicarbonate was contained in the inner sub layer and tartaric acid was in the outer layer.

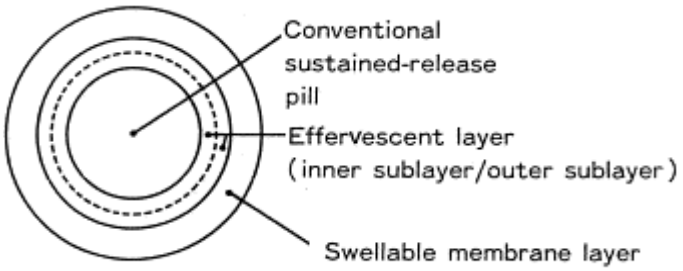

Figure 1.7 Multiple unit oral floating drug delivery system

When the swollen pills are formed, like balloons, they have a density much lower than 1.004 gm/cm^3. The reaction was due to carbon dioxide generated by neutralization in the inner effervescent layer with the diffusion of water through the outer swellable membrane layer.

A floating system utilizing ion-exchange resins has been developed. The system consisted of resin beads, which were loaded with bicarbonate and a negatively charged drug that was bound to the resin. The resultant beads were then encapsulated in a semi permeable membrane to overcome rapid loss of carbon dioxide. Upon arrival in the acidic environment of stomach, an exchange of chloride and bicarbonate ion takes place, as it is expected. As result of this reaction, carbon dioxide was released and trapped in the membrane, thereby, carrying beads toward the top of gastric contents and producing a floating layer of resin beads. In contrast, the uncoated beads sink quickly. Radioactivity measurement by scintigraphy showed that gastric residence was substantially prolonged, compared with a control, when the system was given after a light, mainly liquid meal.

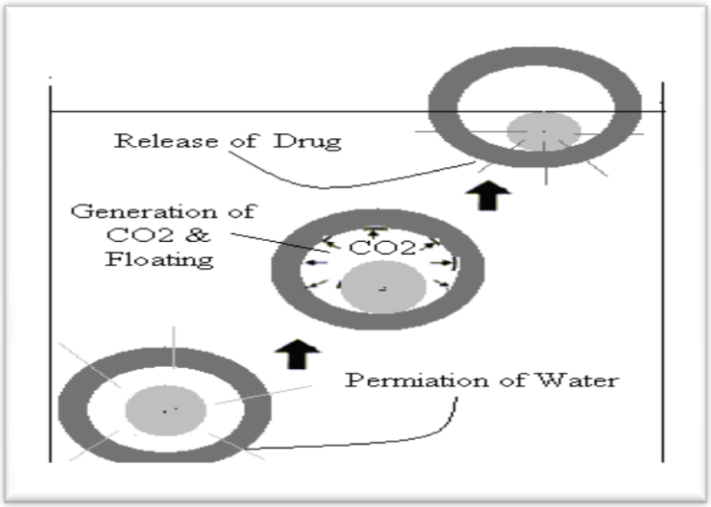

Figure 1.8 Mechanism of effervescent drug delivery system

Furthermore, the system was capable of slow release of drug, a Property which widens the scope of such floating system for SR preparation of drugs possessing negative charge since they can be easily bound to the resin in combination with bicarbonate ions. Two patents on FDDS issued to the Alza Corporation disclosed drug delivery devices for the controlled and continuous administration of medicinal agents. The above figure shows mechanism of floating of effervescent drug delivery system.

b. Inflatable gastrointestinal drug delivery system:

The residence time of the drug delivery device in the stomach can also be sustained by incorporation of an inflatable chamber, which contains a liquid, e.g., ether that gasifies at body temperature to cause the chamber to float in the stomach.

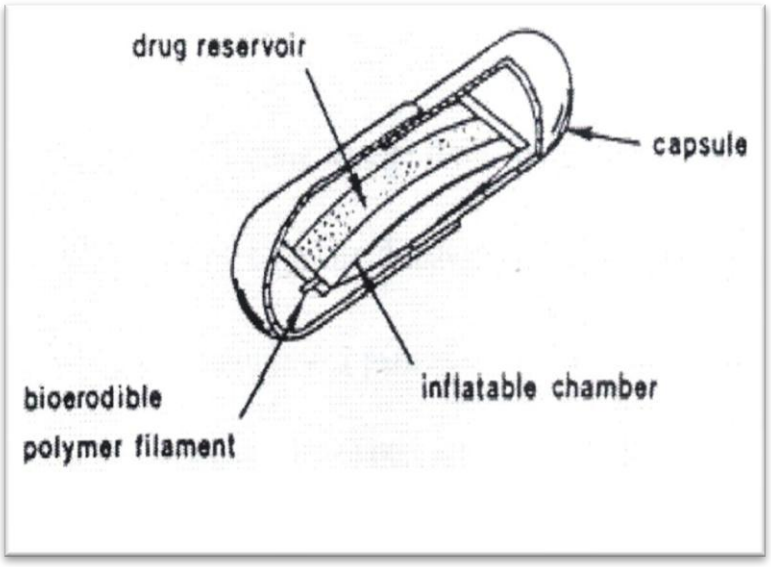

Figure 1.9 Inflatable gastrointestinal drug delivery device

c. Intragastric osmotically controlled drug delivery system:

It is comprised of an osmotic pressure controlled drug delivery and an inflatable floating support in a bio-erodible capsule. When the drug delivery device reaches the site of drug administration e.g. the stomach, the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable floating support is made from a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. Although single unit floating dosage forms have been extensively studied, these single unit dosage forms have the disadvantage of a release all or nothing emptying process while the multiple unit particulate system pass through the GIT to avoid the vagaries of gastric emptying and thus, release the drug more uniformly.

The uniform distribution of these multiple unit dosage forms along the GIT could result in more reproducible drug absorption and reduced risk of local irritation; this gave birth to oral controlled drug delivery and led to development of gastro-retentive floating microspheres.

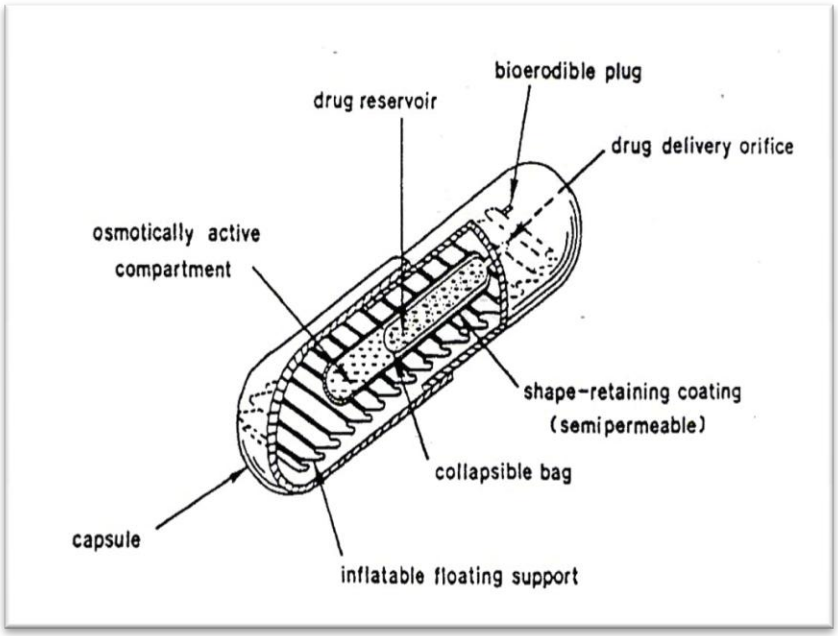

Figure 1.10 Intragasric osmotically controlled drug delivery device.

B. Non-Effervescent FDDS

Floating microsphere are gastro-retentive delivery systems based on non-effervescent approach. Gastro-retentive floating microspheres are low density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. As the system floats over gastric contents, the drug is released slowly at desired rate resulting increased gastric retention with reduced fluctuations in plasma drug concentration. Hollow microspheres are prepared by solvent diffusion and evaporation methods to create the hollow inner core.

a. Hydro dynamically balanced intragastric delivery system

The hydro dynamically balanced gastrointestinal drug delivery systems, in either capsule or tablet form, is designed to prolong GI residence time in an area of the GI tract to maximize drug reaching its absorption site in solution state and hence, ready for

absorption. It is prepared by incorporating a high level (20-75% w/w) of one or more gel-forming hydrocolloids e.g. hydroxyl ethylcellulose, hydroxypropyl cellulose, hydroxyl propyl methyl cellulose and sodium carboxy methyl cellulose into the formulation and then compressing these granules into a tablets.

On contact with gastric fluid the hydrocolloid in this intragatric floating device start to become hydrated and forms a colloid gel barrier around its surface with thickness growing with time. This barrier controls the rate of solvent penetration into the device and the rate of drug release from the device (Figure 1.11). It maintains a bulk density of less than 1 and thus, remains buoyant in the gastric fluid inside the stomach for up to 6 hours.

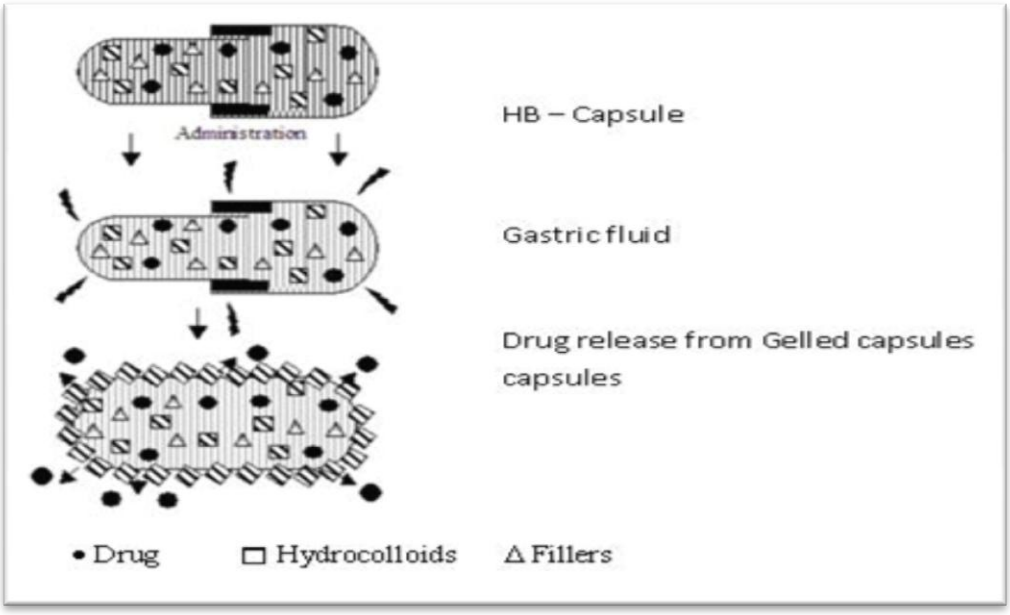

Figure 1.11 Working principle of hydrodynamically balance system

b. Bilayer tablet:

A bilayer tablet can be prepared to contain one immediate–release layer and one

sustained–release layer. After the initial dose is delivered by the immediate release layer, the sustained layer absorbs the gastric fluid and forms a colloidal gel barrier on its surface. This produces a bulk density less than that of the gastric fluid and release remains buoyant in the stomach for extended period of time.

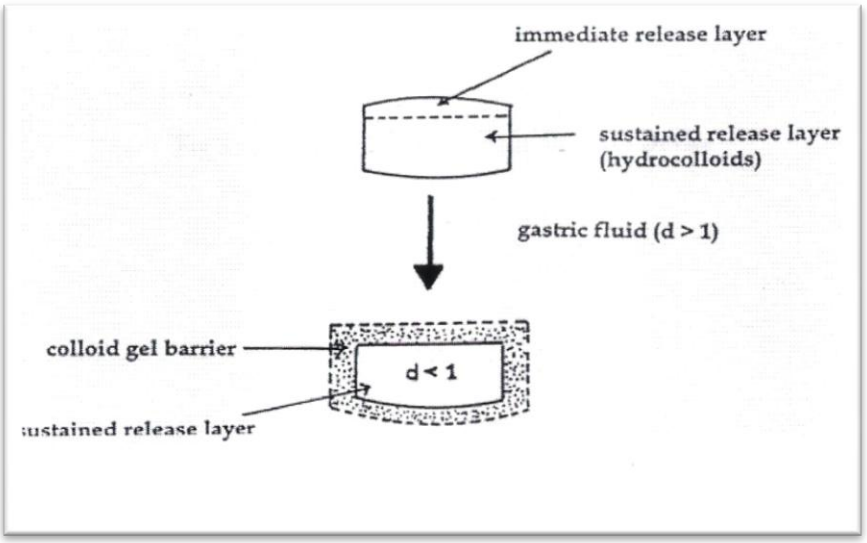

Figure 1.12 Intragastric floating bilayer tablet

c. Intragastric floating gastrointestinal drug delivery system:

A gastrointestinal drug delivery system can be made to float in the stomach by incorporating a floatation chamber, which may be a vacuum or filled with a harmless gas.

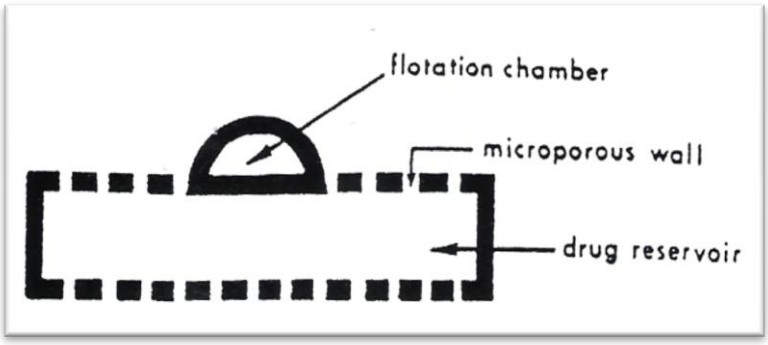

Figure 1.13 Intra-gastric floating drug delivery device

A drug reservoir is encapsulated inside a micro-porous compartment with apertures along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the stomach mucosal surface with the un-dissolved drug. In the stomach the floatation chamber causes the gastrointestinal drug delivery system to float in the gastric fluids. Fluids enter through the apertures, dissolve the drug and carry and drug solute out of the drug delivery system for continuous transport to the intestine for absorption. The other two walls in contact with the fluid are sealed so that undissolved drug remains therein.

1.8 LIMITATIONS OF FDDS *(Mayavanshi A.V. and Gajjar S.S., 2008)*

- The major limitation of floating system is requirement of a sufficient high level of fluids in the stomach for the drug delivery to float. However this limitation can be overcome by coating the dosage form with the help of bio-adhesive polymers that easily adhere to the mucosal lining of the stomach.
- Floating system is not feasible for those drugs that have solubility or stability problem in gastric fluids.
- Drugs which are irritant to gastric mucosa cannot be applicable to GRDFs, floating system.
- The residence time in the stomach depends upon the digestive state. Hence FDDS should be administered after the meal.
- The ability of drug to remain in the stomach depends upon the subject being positioned upright.
- The dosage form should be administered with a minimum of glass full of water (250 ml).

1.9 ADVANTAGES OF FDDS *(Garg R. and Gupta G.D., 2008; Mayavanshi A.V, Gajjar S.S.2008)*

- It is advantageous for drugs absorbed through the stomach, for e.g. Riboflavin.
- It is not restricted to medicaments, which are absorbed from stomach, since it has been found that these are equally efficacious with medicaments which are absorbed from the intestine.
- It is advantageous for drugs meant for local action in the stomach, for e.g. antacids, antiulcer drugs.
- It reduces fluctuations in circulating blood level of drug as shown by the conventional dosage form.
- It shows more uniform levels of drug in plasma.
- It releases drug slowly and for prolonged period of time and hence reduces dosing frequency.
- It increases patient compliance as the dosing frequency is reduced.
- The dissolved drug gets available for absorption in the small intestine after emptying of the stomach contents. It is therefore expected that a drug will be fully absorbed from the floating dosage forms if it remains in the solution.
- Site specific drug delivery.
- Retention of the drug in the GRDF at the stomach minimizes the amount of drug that reaches the colon, hence minimizes adverse activity at the colon.

1.10 APPLICATIONS OF FLOATING DRUG DELIVERY SYSTEMS

(*Bandyopadhyay A.K., 2008; Mayavanshi A.V, Gajjar S.S.,2008)*

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract.

- **Sustained Drug Delivery**

HBS systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. These systems have a bulk density of 1 as a result of which they can float on the gastric contents.

The sustained release floating capsules of nicardipine hydrochloride compared with commercially available MICARD capsules using rabbits. Plasma concentration time curves showed a longer duration for administration (16 hours) in the sustained release floating capsules as compared with conventional MICARD capsules (8 hours).

- **Site-Specific Drug Delivery**

These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, eg, furosemide.

It has been reported that a monolithic floating dosage form with prolonged gastric residence time was developed and the bioavailability was increased. AUC obtained with the floating tablets was approximately 1.8 times those of conventional furosemide tablets.

- **Absorption Enhancement**

Drugs that have poor bioavailability because of site specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption.

1.11 MICROSPHERES *(shobharani., 2008; Kedar Prasad Meena and Danji J.S., et al., 2011)*

Microspheres are solid, approximately spherical particles ranging 1-1000µm in size. They are made up of polymeric substances, in which the drug is dispersed throughout the microsphere matrix. The substances used in the formulation are biodegradable synthetic polymers and natural products. The natural polymers of choice are albumin and gelatin, the synthetic ones being polylactic acid and polyglycolic acid. The polymers used to manufacture microspheres are chosen according to their solubility, stability profile, process, safety and economic suitability.

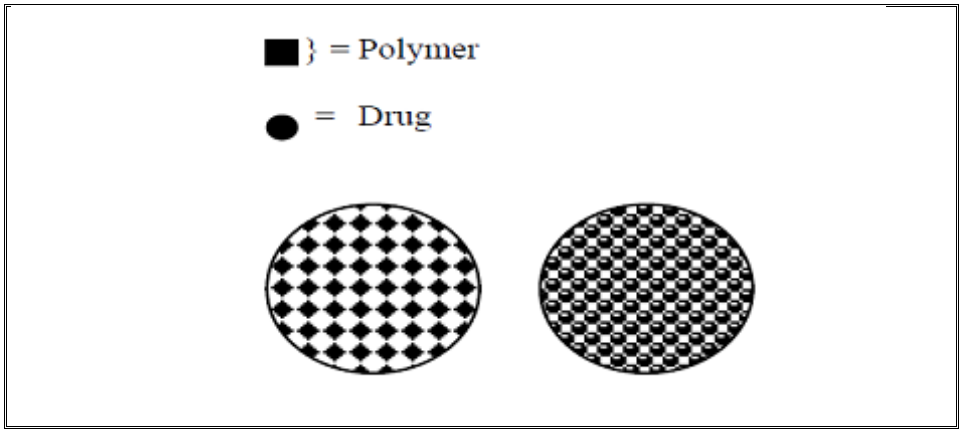

Figure 1.14 Microsphere

Prerequisites for ideal micosphere carriers:

The polymer utilized for the preparation of microspheres should ideally fulfill the following prerequisites:

- ✓ Longer duration of action
- ✓ Control of content release
- ✓ Increase of therapeutic efficacy
- ✓ Protection of drug
- ✓ Reduction of toxicity
- ✓ Biocompatibility
- ✓ Sterilizability
- ✓ Relative stability
- ✓ Water solubility or dispersability
- ✓ Bioresorbability
- ✓ Targetability
- ✓ Polyvalent

AIM AND OBJECTIVE

2. AIM AND OBJECTIVE

Aim:

Oral floating drug delivery system is a suitable drug delivery approach for the drug having low and varied bioavailability e.g. Celecoxib (COX-2 inhibitor) has lesser oral bioavailability and poor absorption in large intestine and poor physicochemical properties like wetting and solubility (Class-II drug according to BCS classification system). Bioavailability of Celecoxib is only 30% when given orally in capsules. The gastro retentive floating microparticulates of Celecoxib would retain the drug in stomach and continuously release the drug in a controlled manner in a predetermined time proposed leading to improved bioavailability. The selection of polymer which is able to release the drug in controlled fashion with initial burst, release of drug to initial therapeutic level quickly.

- Floating sustained release delivery systems for oral dosing are effective in achieving optimal therapy with drugs that have a narrow therapeutic range of blood concentration which eliminate rapidly.
- One of the methods of fabricating sustained release formulations in incorporation of the drug in the floating matrix containing a hydrophilic rate controlling polymer.
- The FDDS is able to prolong the retention time of a dosage form in the stomach, thereby improving the oral bioavailability of the drug.
- These microparticulates are prepared using solvent diffusion and evaporation technique.

Objectives:

- To reduce dosing frequency and improve patient compliance.
- Formulate and evaluate the non-effervescent floating microparticulates of Celecoxib using different synthetic polymers viz. Hydroxy Propyl Methyl Cellulose (HPMC K15M) and Ethyl Cellulose.
- To optimize the concentration of drug-polymer ratio for suitable formulation.
- To characterize the microsphere for its physiochemical properties.
- To evaluate the microsphere for surface characterization with SEM and drug-polymer compatibility study with DSC and FTIR.
- To determine the Buoyancy, Drug Content Uniformity, Drug entrapment efficiency, *in-vitro* drug release studies of microparticulates.
- *In-vitro* drug release kinetic study for release mechanism by the best fit model.
- To determine the *Ex-vivo* permeation studies for best formulation.
- To perform stability studies for best formulation.

PLAN OF WORK

3. PLAN OF WORK

- **LITERATURE REVIEW**
- **SELECTION OF DRUG AND POLYMER**
- **PROCUREMENT OF DRUG AND EXCIPIENTS**
- **EXPERIMENTAL WORK**

a) PREFORMULATION STUDIES

- **Identification of drug**
  - By FTIR spectroscopy
  - By melting point
- **Physicochemical parameters**
  - Organoleptic properties
  - Solubility profile
  - Loss on drying
- **Analytical methods**
  - Determination of λ max
  - Development of standard curve of Celecoxib
  - Determination of percentage purity of drug
- **Determination of compatibility for drug with polymer**
  - By DSC thermal analysis
  - By FTIR Spectroscopy

b) PREPARATION OF NON-EFFERVESCENT FLOATING MICROPARTICULATES

- By solvent diffusion and evaporation method

c) EVALUATION OF NON-EFFERVESCENT FLOATING MICROPARTICULATES

- Appearance
- Percentage Yield
- Micromeritics properties of Non-effervescent floating microparticulates
  - Bulk Density
  - Tapped Density
  - Carr's Compressibility Index
  - Hausner's Ratio
  - Angle of Repose
  - Particle size distribution
- Loss on Drying
- Buoyancy Test
- Entrapment efficiency
- Characterization of microparticulates
  - By scanning electron microscopy
- In-*vitro* Drug release studies
- Kinetics of *In-vitro* drug release
- *Ex-vivo* permeation studies

❖ STABILITY STUDIES

REVIEW OF LITERATURE

4. REVIEW OF LITERATURE

In recent years scientific and technological advancements have been made in the research and development of rate-controlled drug delivery system by overcoming physiological adversities such as short gastric residence time (GRT) and unpredictable gastric emptying time (GET). Several approaches are currently utilized in the prolongation of GRT, including floating drug delivery system (FDDS), also known as hydrodynamically balanced system (HBS), swelling and expanding system, polymeric bioadhesive system, modified shape system, high density system, and other delayed gastric emptying devices.

Literature review indicating advancement in floating drug delivery system is given below:

Margret C.R., *et al.*, (2010) had formulated floating tablets of Itopride hydrochloride using an effervescent approach for gastroretentive drug delivery system. In recent years scientific and technological advancements have been made in the research and development of controlled release oral drug delivery systems by overcoming physiological adversities like short gastric residence times and unpredictable gastric emptying times. The present investigation concerns the development of floating tablets of Itopride hydrochloride, a novel prokinetic drug, which after oral administration are designed to prolong the gastric residence time and thereby increase drug bioavailability, and drug release rate. Floating tablets were fabricated; using direct compression method;

containing Itopride hydrochloride, polymers HPMC K100M, HPMC K15M and Carbopol 934P.

Vishal G.K., *et al.,* (2010) had prepared a Floating tablet of Furosemide (FUR) by direct compression technique. Furosemide was chosen as model drug because it is slightly soluble in water and poorly absorb from lower intestine. PEG-6000 is used as carrier agent for increasing solubility of Furosemide in water. Hydroxypropyl methylcellulose, sodium bicarbonate and carbopol were used as matrixing agent, gas generating agent and floating agent respectively.

Dhawale S.C., *et al.,* (2009) had developed and evaluated floating drug delivery system of Acyclovir. Gastric floating drug delivery was employed to develop controlled release preparation. Sodium bicarbonte as gas generating agent dispersed in a hydrogel matrix. The matrix was a mixture of HPMC K4M, HPMC K100M and xanthan gum.

Dalavi V.V., *et al.,* (2009) had developed gastroretentive drug delivery system of an antiretroviral agent of Zidovudine to achieve the objective, 3×3 factorial design were chosen. In this design amount of HPMC K4M (X1) and gas generating agents (X2) were selected as independent variable. The time required for 50% drug release t50% (Y1) was selected as dependent variable. The derived polynomial equations for t50%were verified by two check point formulations. The results of factorial design showed that factor X1 and X2 significantly affect the studied dependent variables. The formulation with good floating time (24 hrs) and the percent drug release (98.05 %) emerged as optimal.

Kishan V., *et al.*, (2009) had developed Floating matrix tablets of Norfloxacin to prolong gastric residence time, leading to an increase in drug bioavailability. Tablets were prepared by the wet granulation technique, using polymers such as Hydroxy propyl methyl cellulose (HPMC-K4M, HPMC-K100M) and Xanthan gum.

Prakash R.C., *et al.*, (2009) had formulated and optimizes the floating drug delivery systems containing cephalexin using 23 factorial design. Floating tablets were prepared by direct compression method incorporating HPMC K4M, Xanthan Gum, Guar Gum, Sodium bicarbonate and tartaric acid as a gas generating agent. The influences of independent variables like polymer polymer ratio polymer type on floating lag time and cephalaxin release profiles were studied.

Kshirsagar R.V., *et al.*, (2009) had developed a hydro dynamically balanced system of metformin as a single unit floating tablet. Various grades of low-density polymers were used for the formulation of this system. They were prepared by physical blending of metformin and the polymers in varying ratios. The formulation was optimized on the basis of *in-vitro* buoyancy and *in-vitro* release in simulated gastric fluid pH 1.2. Effect of Carbopol as a release modifier was studied to ensure the delivery of drug from the floating tables over a prolonged time period. Tablets prepared with HPMC K15M and Carbopol gave the best *in-vitro* percentage release and were taken as the optimized formulation.

Rajesh K., *et al.*, (2009) had been prepared ranitidine hydrochloride sustained release formulation for 24 hrs. Various formulations were prepared by wet granulation technique using the polymers, such as HPMC K100M and HPMC K15M. It was found that the best formulation for RT8 was having the floating lag time of 120 sec and showed 98.4% drug release at the end of 24 hours. *In-vitro* drug release studies of Ranitidine hydrochloride sustained release floating tablets showed that, the rate of drug release is diffusion controlled and follows zero order kinetics.

Sauzet C., *et al.*, (2009) had formulated different technologies intended for gastro retentive dosage delivery were investigated and patented. The aim of this study was to develop an innovative floating gastro retentive dosage form (GRDF). The developed technology induces a low-density dosage form containing high active pharmaceutical ingredient (API) concentration by using a hydrophobic dusty powder excipient under specific conditions. The new dosage form was obtained by state of the art wet granulation manufacturing process. An apparatus was developed to measure the apparent density of floating tablet. The GRDF was characterized for apparent density, buoyancy, porosity and dissolution using *in-vitro* experimentations.

Anand P., *et al.*, (2009) had developed a novel gastro retentive controlled release drug delivery system of verapamil HCl was formulated in an effort to increase the gastric retention time of the dosage form and to control drug release. Hydroxy propyl methyl cellulose (HPMC), carbopol, and xanthan gum were incorporated for gel forming properties. Buoyancy achieved by adding an effervescent mixture of sodium bicarbonate

and anhydrous citric acid. *In-vitro* drug release studies were performed, and drug release kinetics was evaluated using the linear regression method.

Ajit K., *et al.,* (2009) design bilayer regioselective floating tablets of Atenolol and Lovastatin to give immediate release of Lovastatin and sustained release of Atenolol. Bilayer floating tablets comprised two layers, i.e immediate release and controlled release layers. The immediate release layer comprised sodium starch glycollate as a super disintegrant and the sustained release layer comprised HPMC K100M and xanthan gum as the release retarding polymers. Sodium bicarbonate was used as a gas generating agent. Direct compression method was used for formulation of the bilayer tablets. Accelerated stability studies were carried out on the prepared tablets in accordance with ICH guidelines. All formulations floated for more than 12 hrs. More than 90% of Lovastatin was released within 30 min. Diffusion exponents (n) were determined for all the formulations (0.53-0.59). The release of Atenolol was found to follow a mixed pattern of Korsmeyer-Peppas, Hixson- Crowell and zero order release models. The optimized formulation was found to be buoyant for 8 hrs in stomach. Therefore, biphasic drug release pattern was successfully achieved through the formulation of floating bilayer tablets in this study.

Prajapati S.T., *et al.,* (2009) developed gastric floating matrix tablet of Domperidone. Box-Behnken design was employed in formulating gastric floating drug delivery system using three polymers HPMC (K4M), Carbopol 934P, Sodium alginate as independent variables. HPMC loading was found to be significant for floating properties.

No significant effect of Sodium alginate on floating properties was observed but it was important for gel formation. The quadratic mathematical model developed could be used to predict formulations with desired release and floating properties.

Thakkar V.T., *et al.,* (2008) had developed and evaluates the Levofloxacin hemihydrates floating formulations (F1-F9). Selection of optimized batch was done by model dependent approach and novel mathematical approach. F1-F9 batches were prepared by direct compression method using Gelucire 43/01 (hydrophobic) and hydroxy propyl methyl cellulose (hydrophilic) polymer in different ratios. The floating tablets were evaluated for uniformity of weight, hardness, friability, drug content, *in-vitro* buoyancy and *in-vitro* release studies. Various models were used to estimate kinetics of drug release.

Jaimini M., *et al.,* (2007) had formulated and evaluated floating tablets of Famotidine which were prepared by effervescent approach using two different grades of Methocel K100 and K15M. The tablets with Methocel K100 were found to float for longer duration as compared with formulations containing Methocel K15M. The drug release from the tablets was sufficiently sustained and non-Fickian transport of the drug from tablets was confirmed.

Shishu N., *et al.,* (2007) 5-Fluorouracil (5-FU) has been the most widely used drug for the chemotherapy of gastrointestinal cancer for many decades. The present investigation concerns the development and evaluation of single unit floating tablets of 5-

FU which, after oral administration, are designed to prolong the gastric residence time, increase drug bioavailability and target the stomach cancer. A floating drug delivery system (FDDS) was developed using gas-forming agents, like sodium bicarbonate, citric acid and hydrocolloids, like hydroxyl propyl methyl cellulose (HPMC) and Carbopol 934P. The formulations were optimized for the type of filler, like lactose, microcrystalline cellulose (MCC) and dicalcium phosphate (DCP) as well; different viscosity grades of HPMC and concentrations.

Sanjay S.P., *et al.*, (2006) had developed floating matrix tablets are designed to prolong the gastric residence time after oral administration, at a particular site and controlling the release of drug especially useful for achieving controlled plasma level as well as improving bioavailability. With this objective, floating dosage form containing clarithromycin as drug was designed for the treatment of *Helicobacter pylori*. Incorporation of gas-generating agent together with polymer improved drug release, besides optimal floating (floating lag time <30 s; total floating time >10 h).

Patel V.F, *et al.*, (2006) developed intragastric floating drug delivery system of Cefuroxime axetil and carried out its *in-vitro* evaluation and employed 32 full factorial designs to evaluate contribution of HPMC and SLS on drug release. Tablets were prepared using direct compression technique. Multiple regression analysis was performed for factorial design batches to evaluate the response. All formulations had floating lag times below 2 minutes and constantly floated on dissolution medium for more than 8

hours. Also linear relationships were obtained between the amount of HPMC K100 LV and diffusion exponent as well as release rate constant.

Dave B.S., *et al.*, (2004) had prepared a floating tablet of Ranitidine hydrochloride by using guar gum, xanthan gum and hydroxylpropyl methylcellulose, Sodium bicarbonate was incorporated as gasgenerating agent. It is prepared by direct compression method and *in-vitro* study done into 0.1 N HCl as dissolution medium. Drug release was calculated by Higuchi and Peppas models.

Hoffman A., *et al.*, (2003) Expandable gastroretentive dosage forms (GRDFs) have been designed for the past 3 decades. They were originally created for possible veterinary use, but later the design was modified for enhanced drug therapy in humans. These GRDFs are easily swallowed and reach a significantly larger size in the stomach due to swelling or unfolding processes that prolong their gastric retention time (GRT). Positive results were obtained in preclinical and clinical studies evaluating GRT of expandable GRDFs.

Kim H. K., *et al.*, (2000) has studied the scientific and technological advancements have been made in the research and development of rate-controlled oral drug delivery systems by overcoming physiological adversities, such as short gastric residence times (GRT) and unpredictable gastric emptying times (GET). Several approaches are currently utilized in the prolongation of the GRT, including floating drug

delivery systems (FDDS), also known as hydrodynamically balanced systems (HBS), swelling and expanding systems, polymeric bioadhesive systems.

Baumgartner S., *et al.*, (2000) had developed a matrix-floating tablet incorporating high dose of freely soluble drug. The formulation containing 54.7% of drug, HPMC K4 M, Avicel PH 101 and a gas-generating agent had given the best results. It required 30 seconds to become buoyant. *In-vivo* experiments with fasted state in beagle dogs revealed prolonged gastric residence time. On radiographic images taken after 30 minutes of administration, the tablet was observed in animal stomach and the next image taken at 1 hr showed that the tablet had altered its position and turned around. The comparison of gastric motility and stomach emptying between humans and dogs showed no big difference hence it was speculated that the experimentally proven increased gastric residence time in dogs than humans.

Literature review indicating work carried out on selected drug, Celecoxib is given below:

Satish Singh, *et al.*, (2012) has been formulated non effervescent gastroretentive floating drug delivery of Celecoxib to increase therapeutic efficacy, reduce frequency of administration and improve patient compliance. Solvent evaporation was used to prepare the microparticulates and evaluated for buoyancy, density, particle size, SEM, *in-vitro* dissolution, *in-vitro* permeation and *in-vivo* studies. Polymers Ethyl Cellulose, Dibutyl

Phthalate and Methocel were used. *In-vitro* drug release was performed for 8 hours and the percentage drug release was found to be 52.58% to 61.57%

Punitha, et al, (2009) has studied to improve the physicochemical properties of celecoxib like solubility, dissolution properties and stability of poorly soluble drug by forming dispersion with urea as water soluble carrier. The solid dispersion of celecoxib by physical triturating method, Solvent evaporation and fusion method were prepared using 1:1, 1:3 and 1:5 ratios of drug and polymer (urea). The saturation solubility was carried using USP type XXIV (paddle) type dissolution apparatus. The prepared dispersion showed marked increase in the saturation solubility and dissolution rate of celecoxib than that of pure drug. The dispersion with urea (1:5) by fusion method showed faster dissolution rate (79.08%) as compared to other dispersions with urea (1:1 and 1:3) whichever prepared by physical mixture and solvent evaporation method. Solid dispersion of celecoxib: urea prepared as 1:5 ratio by fusion method showed excellent physicochemical characteristics and was found to be described by dissolution release kinetics and was selected as the best formulation in this study.

Karade Preeti, et al (2012) has developed a topical gel formulation of celecoxib, which would attenuate the gastrointestinal relater toxicities associated with oral administration and to investigate the effect of DMSO on permeation of celecoxib. Gel with different concentrations of carbapol, sodium alginate and sodium carboxy methylcellulose were prepared. Gels were subjected for various evaluation tests such as pH measurement, spreadibility and extrudability. *In-vitro* dissolution studies were

performed in phosphate buffer of pH 5.6 and polyethylene glycol 400 (7.4 pH) for 12 hrs by using Keshary-Chien diffusion cell apparatus. The gel formulation consisting of 7.5% w/w sodium alginate with DMSO found to be suitable for topical application based on *in-vitro* evaluation. Sodium alginate based gels with DMSO revealed of 90% cumulative drug release after 12 hours. From the above observations, Sodium alginate seems to be a promising pharmaceutical adjuvant in the formulation of celecoxib gels.

Mohammed Mostafa Ibrahim, et al., (2013), Celecoxib-loaded NPs were prepared from biodegradable polymers such as poly-caprolactone (PCL), poly(L-lactide) (PLA), and poly(D,L-lactide-*co*-glycolide) by spontaneous emulsification solvent diffusion method. Nanoparticles (NPs) were characterized regarding their particle size, PDI, zeta potential, shape, morphology, and drug content. Celecoxib-loaded NPs were incorporated into eye drops, *in situ* gelling system, and gel and characterized regarding their pH, viscosity, uniformity of drug content, *in-vitro* release, and cytotoxicity.

Shahzad, et al., (2012), employed response surface methodology (RSM) for statistical optimization of formulation factors in the preparation of celecoxib-loaded microspheres. Celecoxib microspheres were prepared by solvent evaporation method. Biodegradable/biocompatible polymers, Eudragit L-100 and polyvinyl pyrrolidone, were used in the encapsulation procedure. The microspheres were characterized for size, shape, recovery (%), entrapment efficiency and drug release. Using RSM, Celecoxib-loaded microsphere formulation with optimum recovery, entrapment efficiency and release behavior was proposed.

DRUG AND EXCIPIENTS PROFILE

5. DRUG AND EXCIPIENTS PROFILE

5.1. DRUG PROFILE:

CELECOXIB: (*USP, 2012; http://www.drugbank.ca/drugs/DB00482)*

Celecoxib is a Non-Steroidal anti-inflammatory drug (NSAID). This drugs is still among the most widely used drugs in the world. Celecoxib is used in the treatment of pain and inflammation, associated with rheumatoid arthritis, and several other inflammatory disorders. Celecoxib is a COX-2 specific inhibitor, promoting a reduction of the inflammatory process and maintaining normal physiological levels of prostanoids in stomach and kidneys. It appears to have a gastrointestinal safety profile superior to the traditional NSAID.

A. IUPAC Name: 4-[5- (4- methyl phenyl) - 3- (trifluoro methyl) - 1H-pyrazol- 1-yl] benzene sulfonamide

B. Molecular Structure:

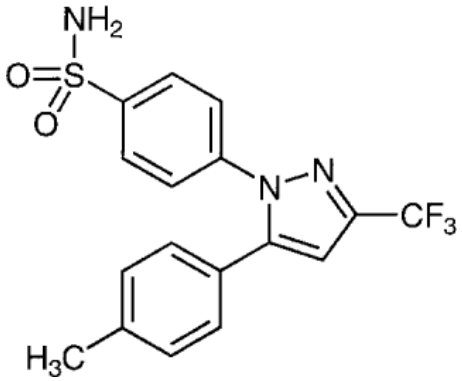

Figure 5.1 Molecular structure of Celecoxib

C. Category: Non-Steroidal Anti-Inflammatory Drug (NSAID).

- First specific inhibitor of cyclo-oxygenase-2 (COX-2)

D. Molecular formula: $C_{17}H_{14}F_3N_7O_2S$

E. Molecular weight: 381.37

F. Description: White or almost white, crystalline or amorphous powder.

G. Solubility: Soluble to freely soluble in ethanol; soluble in Methylene chloride; practically insoluble in water.

H. Melting Range: 161.3℃ to 162.2℃

I. Peak Plasma concentration: 3 hours

J. Recommended daily Dose: 200 mg taken once daily or in two divided doses.

K. Pharmacokinetics:

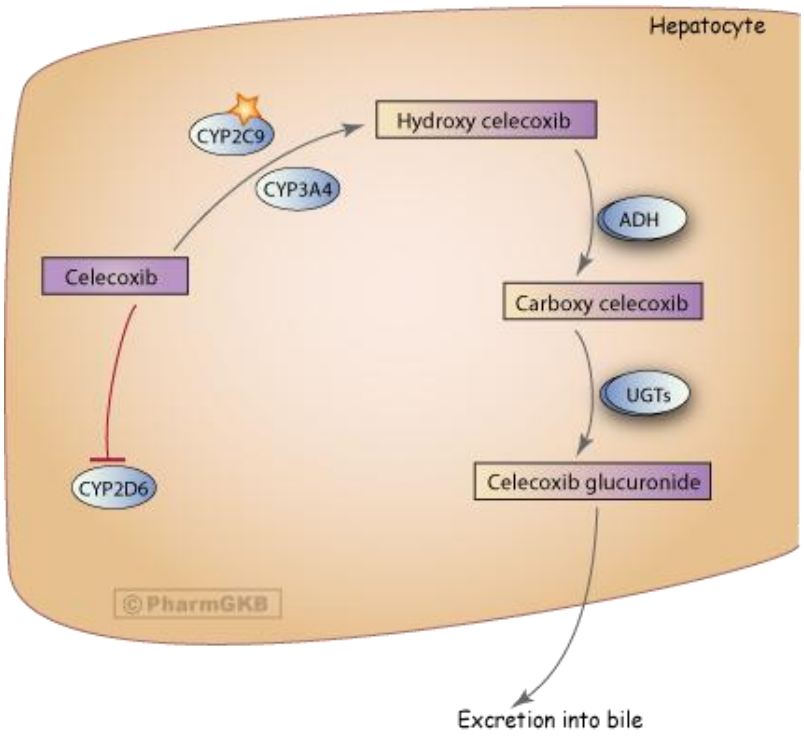

Figure 5.2 Hepatic metabolism of Celecoxib

After oral administration, Celecoxib is rapidly absorbed and achieves peak serum concentration in about 3 hours. It is extensively metabolized in the liver with very little drug (<3 %) being eliminated unchanged. The major routes of excretion for Celecoxib are feces and urine. Celecoxib is metabolized primarily through methyl hydroxylation to form hydroxycelecoxib. This reaction is largely catalyzed by CYP2C9, although CYP3A4 also plays a minor (<25 %) role. Hydroxy-celecoxib is further oxidized to form carboxy-celecoxib via cytosolic alcohol dehydrogenases ADH1 and ADH2, then conjugated with glucuronic acid via UDP glucuronosyl transferases (UGT's) to form the 1-O-glucuronide. None of the metabolites are pharmacologically active.

L. PHARMACOKINETICS DATA:

- **Bioavailability**: approx 43%
- **Apparent volume of distribution:** 455±166 Liters
- **Half-life**: 11 hours
- **Metabolism**: Celecoxib is metabolized in liver. Celecoxib metabolism is primarily mediated vis cytochrome P450 2C9. Three metabolites, a primary alcohol, the corresponding carboxylic acid and its glucoronide conjugate,have been identified in human plasma. These metabolites are inactive as COX-1 or COX-2 inhibitors in *in-vitro* models.
- **Excretion**: Feces and Urine. Celecoxib is eliminated predominantly by hepatic metabolism with little (<3 %) unchanged drug recovered in the urine and feces.
- **Plasma protein binding:** Highly Plasma protein bound (approx 97 %)

M. Pharmacodynamics:

Celecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, is classified as a non-steroidal anti-inflammatory drug (NSAID). Celecoxib is used to treat rheumatoid arthritis, osteoarthritis, and familial adenomatous polyposis (FAP). Because of its lack of platelet effects, Celecoxib is not a substitute for aspirin for cardiovascular prophylaxis. It is not known if there are any effects of Celecoxib on platelets that may contribute to the increased risk of serious cardiovascular thrombotic adverse events associated with the use of Celecoxib. Inhibition of PG-E2 synthesis may lead to sodium and water retention through increased reabsorption in the renal medullary thick ascending loop of Henle and perhaps other segments of the distal nephron. In the collecting ducts, PG-E2 appears to inhibit water reabsorption by counteracting the action of antidiuretic hormone.

N. Mechanism of action:

The mechanism of action of celecoxib is believed to be due to inhibition of prostaglandin synthesis. Unlike most NSAID's, which inhibit both types of cyclo-oxygenases (COX-1 and COX-2), Celecoxib is a selective noncompetitive inhibitor of cyclooxygenase-2 (COX-2) enzyme. It binds with its polar sulfonamide side chain to a hydrophilic side pocket region close to the active COX-2 binding site. Both COX-1 and COX-2 catalyze the conversion of arachidonic acid to prostaglandin (PG) H2, the precursor of PGs and thromboxane.

O. Indications:

- Osteoarthritis
- Rheumatoid Arthritis
- Ankylosing Spondylitis
- Acute pain
- Primary Dysmenorrhea
- Adenomatous Polyposis

P. Adverse effects:

Symptoms of overdose include breathing difficulties, coma, drowsiness, gastrointestinal bleeding, high blood pressure, kidney failure, nausea, sluggishness, stomach pain, and vomiting.

Q. Drug interactions:

- Celecoxib may increase the anticoagulant effect of acenocoumarol, anisindione and dicumarol.
- Fluconazole may increase the effect of celecoxib.
- Bile acid sequestrants may decrease the absorption of Nonsteroidal Anti-Inflammatory Agents.
- The COX-2 inhibitor increases serum levels of lithium.
- Concomitant use of Telmisartan and Celecoxib may increase the risk of acute renal failure and hyperkalemia.
- Celecoxib, may reduce the antihypertensive effect of Trandolapril.
- Tolbutamide, a strong CYP2C9 inhibitor, may decrease the metabolism and clearance of Celecoxib.

R. Dosage forms

- Capsules: 50mg, 100mg, 200mg and 400mg

5.2 EXCIPIENTS PROFILE

HYPROMELLOSE (Hydroxy Propyl Methyl Cellulose) *(Rowe R.C., et al., 2003)*

A. Nonproprietary Names:

BP: Hypromellose JP: Hydroxypropylmethylcellulose

PhEur: Hypromellosum USP: Hypromellose

B. Synonyms:

Benecel MHPC; E464; hydroxypropyl methylcellulose; HPMC; *Methocel*; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; *Metolose*; *Tylopur*.

C. Chemical Name and CAS Registry Number:

Cellulose hydroxyl propyl methyl ether [9004-65-3]

D. Molecular Weight:

Molecular weight is approximately 10,000 to 1,500,000.

E. Structural Formula:

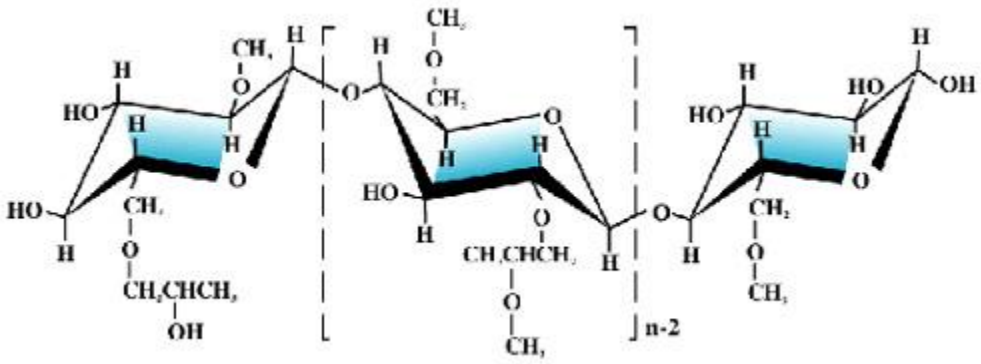

Figure 5.3 Structural formula of Hypromellose

F. Functional Category:

Coating agent, Film-former, Rate-controlling polymer for sustained release, Stabilizing agent, Suspending agent, Tablet binder, Viscosity-increasing agent.

G. Applications in Pharmaceutical Formulation or Technology:

Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations. In oral products, Hypromellose is primarily used as a tablet binder, in film-coating, and as matrix for use in extended-release tablet formulations. High viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Lower-viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents.

H. Description:

Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder.

I. Typical Properties:

- **Acidity/alkalinity** **:** pH = 5.5–8.0 for a 1% w/w aqueous solution.
- **Density (bulk)** **:** 0.341 g/cm^3
- **Density (tapped)** **:** 0.557 g/cm^3
- **Density (true)** **:** 1.326 g/cm^3
- **Melting point** **:** browns at 190–200°C; chars at 225–230°C.
- **Glass transition temperature:** 170–180°C.

- **Moisture content:** Hypromellose absorbs moisture from the atmosphere; the amount of water absorbed depends upon the initial moisture content and the temperature and relative humidity of the surrounding air.
- **Solubility:** Soluble in cold water, forming a viscous colloidal solution. Practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol.
- **Viscosity (dynamic):** A wide range of viscosity types are commercially available.

Table 5.1 Typical viscosity values for 2% w/v aqueous solutions of Methocel at 20°C.

***Methocel* product**	**USP 28 designation**	**Nominal viscosity (mPa s)**
Methocel K100 Premium LVEP	2208	100
Methocel K4M Premium	2208	4000
Methocel K15M Premium	2208	15 000
Methocel K100M Premium	2208	100 000
Methocel E4M Premium	2910	4000
Methocel F50 Premium	2906	50
Methocel E10M Premium CR	2906	10 000
Methocel E3 Premium LV	2906	3
Methocel E5 Premium LV	2906	5
Methocel E6 Premium LV	2906	6
Methocel E15 Premium LV	2906	15
Metolose 60SH	2910	50, 4000, 10 000
Metolose 65SH	2906	50, 400, 1500, 4000
Metolose *90SH*	2208	100, 400, 4000, 15 000

Aqueous solutions are most commonly prepared, although Hypromellose may also be dissolved in aqueous alcohols such as ethanol and propan-2-ol provided the alcohol content is less than 50% w/w.

J. Stability and Storage Conditions

Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3–11. Increasing temperature reduces the viscosity of solutions. Hypromellose undergoes a reversible sol–gel transformation upon heating and cooling, respectively.

K. Incompatibilities

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts.

ETHYL CELLULOSE: *(Rowe R.C., et al., 2003; http://www.ethocel.com)*

A. Nonproprietary Names:

BP: Ethyl cellulose USP-NF: Ethyl cellulose

PhEur: Ethylcellulosum

B. Synonyms:

Aquacoat ECD; Aqualon; E462; Ethocel; Surelease.

C. Chemical Name and CAS Registry Number:

Cellulose ethyl ether [9004-57-3].

D. Structural Formula:

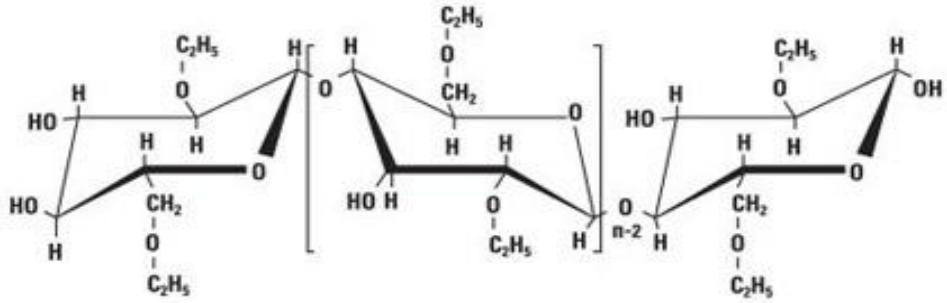

Figure 5.4 Structural formula of Ethyl cellulose

E. Functional Category:

Coating agent, Flavoring fixative, Tablet binder, Tablet filler, Viscosity-increasing agent.

F. Applications in Pharmaceutical Formulation or Technology:

Ethyl cellulose is a derivative of cellulose in which some of the hydroxyl groups on the repeating glucose units are converted into ethyl ether groups.

Table 5.2: Use of Ethyl cellulose depending on concentration

Use	Concentration (%)
Microencapsulation	10.0–20.0
Sustained-release tablet coating	3.0–20.0
Tablet coating	1.0–3.0
Tablet granulation	1.0–3.0

The number of ethyl groups can vary depending on the manufacturer. It is widely used as a thin-film coating material. It is also used as a food additive as an emulsifier. Ethyl cellulose is widely used in oral and topical pharmaceutical formulations.

G. Description:

Ethyl cellulose is an odorless and tasteless, white powder.

H. Typical Properties:

- **Density (bulk)** **:** 0.4 g/cm^3
- **Melting point** **:** 165 - 173℃.
- **Glass transition temperature** **:** 129–133℃.
- **Specific gravity** **:** 1.12–1.15 g/cm^3

- **Moisture content:** Ethyl cellulose absorbs very little water from humid air or during immersion, and that small amount evaporates readily.
- **Solubility:** Ethyl cellulose is practically insoluble in glycerin, propylene glycol, and water. Ethyl cellulose that contains less than 46.5% of ethoxyl groups is freely soluble in chloroform, methyl acetate, and tetrahydrofuran, and in mixtures of aromatic hydrocarbons with ethanol (95%). Ethyl cellulose that contains not less than 46.5% of ethoxyl groups is freely soluble in chloroform, ethanol (95%), ethyl acetate, methanol, and toluene.
- **Viscosity:** Viscosity of ethyl cellulose is measured typically at 25℃ using 5% w/v ethyl cellulose dissolved in a solvent blend of 80% toluene: 20% ethanol (w/w). Grades of ethyl cellulose with various viscosities are commercially available. They may be used to produce 5% w/v solutions in organic solvent blends with viscosities

nominally ranging from 7 to 100 mPa s (7–100 cP). Specific ethyl cellulose grades, or blends of different grades, may be used to obtain solutions of a desired viscosity. Solutions of higher viscosity tend to be composed of longer polymer chains and produce strong and durable films. The viscosity of an ethyl cellulose solution increases with an increase in ethyl cellulose concentration; e.g. the viscosity of a 5% w/v solution of Ethocel Standard 4 Premium is 4 mPa s (4 cP) and of a 25% w/v solution of the same ethyl cellulose grade is 850 mPa s (850 cP). Solutions with a lower viscosity may be obtained by incorporating a higher percentage (30–40%) of a low-molecular-weight aliphatic alcohol such as ethanol, butanol, propan-2-ol, or n-butanol with toluene. The viscosity of such solutions depends almost entirely on the alcohol content and is independent of toluene. In addition, non-pharmaceutical grades of ethyl cellulose that differ in their ethoxyl content and degree of polymerization are available.

MATERIALS AND EQUIPMENTS

6. MATERIALS AND EQUIPMENTS

6.1: Raw materials

Table 6.1: Raw materials with name of the supplier

S.No	Name of Raw material	Name of the supplier
1	Celecoxib	Alembic Limited, Gujarat.
2	HPMC K15M	Griffon laboratories Pvt. Ltd., Mumbai.
3	Ethyl cellulose	Griffon laboratories Pvt. Ltd., Mumbai.
4	Dichloromethane	S.D fine-chem limited, Mumbai.
5	Dimethyl formamide	S.D fine-chem limited, Mumbai.
6	Liquid paraffin	Qualigens fine chemicals, Mumbai.
7	Tween 80	Qualigens fine chemicals, Mumbai.
8	Petroleum ether	S.D fine-chem limited, Mumbai.

6.2: Equipments

Table 6.2: Equipments with Make and Model

S.No	Name of the Equipments	Make and Model
1	Electronic balance	Shimadzu BL-220H
2	Digital pH meter	ELICO-LI120
3	Mechanical Stirrer	Remi equipments limited, Mumbai
4	Magnetic Stirrer	Remi equipments limited, Mumbai
5	UV Visible Spectrophotometer	ELICO SL159
6	USP tablet dissolution apparatus	Veego scientific VDA-8DR
7	Scanning electron microscope	Model-S-3400N, SEM HITACHI
8	UV visible spectrophotometer	Shimadzu-1700 Pharmaspec UV visible spectrophotometer
9	FTIR spectrophotometer	Shimadzu S4008
10	Differential scanning calorimeter	Shimadzu DSC 60, Japan
11	Particle size analyzer	Malvern Particle size analyzer (Master Seizer 2000)

EXPERIMENTAL WORK

7. EXPERIMENTAL WORK

7.1 Preformulation studies

Preformulation testing was an investigation of physical and chemical properties of a drug substance alone. It was the first step in rational development of dosage form.

7.1.1. Identification of drug

A] By FTIR spectroscopy *(IP, 2007)*

Celecoxib discs were prepared by pressing the Celecoxib with potassium bromide and the spectra between 4000^{-1} to 500^{-1} cm was obtained under the operational conditions. The absorption maximums in spectrum obtained with the substance being examined correspond in position and relative intensity to those in the reference spectrum in Table 8.1 and Figure 8.1

B] By melting point *(IP, 2007)*

Melting point of the drug was determined by capillary tube method.

7.1.2. Physicochemical parameters

A] Organoleptic properties *(Lachman L., et al., 1991; Bankar G.S. and Rhodes C.T., 1996)*

The color, odor and nature of the drug were recorded using descriptive terminology.

B] Solubility study *(Merck Index, IP, 2007)*

It is important to know about solubility characteristic of a drug in aqueous system, since they must possess some limited aqueous solubility to elicit a therapeutic response. The solubility of drug was recorded by using various descriptive terminology specified in Indian pharmacopoeia, 2007. The solubility study was shown in Table 8.4.

Table: 7.1. Values for estimating drug solubility based upon "USP definition"

Descriptive Term	Appropriate volume of solvent in milliliters per gram of solute
Very soluble	Less than 1 part solvent needed to dissolve 1 part solute
Freely soluble	From 1 to 10 parts solvent needed to dissolve 1 part solute
Soluble	From 10 to 30 parts solvent needed to dissolve 1 part solute
Sparingly soluble	From 30 to 100 parts solvent needed to dissolve 1 part solute
Slightly soluble	From 100 to 1000 parts solvent needed to dissolve 1 part solute
Very slightly soluble	From 1000 to 10,000 parts solvent needed to dissolve 1 part solute
Practically insoluble	More than 10,000 parts solvent needed to dissolve 1 part solute

C] Loss on drying *(IP, 2007)*

Loss on drying is the loss of weight expressed as percentage w/w resulting from water and volatile matter of any kind that can be driven off under specified condition. The accurately weighed 1 gm of sample was transferred in stoppered-glass shallow weighing bottle and accurately weighed the bottle. The bottle was transferred in oven and substance was dried at 105°C for 3 hours. The bottle was removed from oven and reweighed. Loss on drying was calculated by following equation. It was shown in Table 8.5

$$\text{Loss on Drying} = \frac{\text{[Initial Weight of sample taken - Final Weight of sample after drying]}}{\text{Initial Weight of sample taken}} \times 100$$

7.1.3. Determination of λ max *(Fabián Teixeira Primo., et al., 2005)*

The absorption maximum of the standard solution was scanned between 200-400 nm regions on UV-VISIBLE spectrophotometer. The absorption maximum obtained with the substance being examined corresponds in position and relative intensity to those in the reference spectrum.

Preparation of 0.2 N sodium hydroxide:

Dissolve 8 gm of sodium hydroxide in water and allow to stand and finally make up the volume to 1000 ml.

Procedure for determination of λ max using 0.2 N sodium hydroxide:

50 mg of Celecoxib was weighed accurately and transferred into 50 ml volumetric flask and dissolved in 0.2 N NaOH, after dissolution the volume was made up to the mark with 0.2 N NaOH (1000 µg/ml). Further dilution was made by pipetting 10 ml into 100 ml volumetric flasks to acquire 100 µg/ml solution made up with 0.2 N NaOH. Further dilution was made by pipetting 3 ml into 25 ml volumetric flasks to acquire 12 µg/ ml solution made up with 0.2 N NaOH.

Preparation of Simulated Gastric Fluid (without Enzyme):

Dissolve 2 g of Sodium chloride in water. Add 7 mL of Hydrochloric Acid and sufficient water to make 1000 mL.

Procedure for determination of λ max using Simulated Gastric Fluid (without Enzyme):

50 mg of Celecoxib was weighed accurately and transferred into 50 ml volumetric flask and dissolved in 3 ml of methanol, after dissolution the volume was made up to the mark with Simulated Gastric Fluid (without Enzyme) (1000 µg/ml). Further dilution was made by pipetting 10 ml into 100 ml volumetric flasks to acquire 100 µg/ml solution made up with Simulated Gastric Fluid (without Enzyme). Further dilution was made by pipetting 3 ml into 25 ml volumetric flasks to acquire 12 µg/ ml solution made up with Simulated Gastric Fluid (without Enzyme).

7.1.4. Development of standard curve of Celecoxib *(Fabián Teixeira Primo., et al., 2005)*

Standard curve of Celecoxib in 0.2 N Sodium Hydroxide:

50 mg of Celecoxib was weighed accurately and transferred into 50 ml volumetric flask and dissolved in 0.2 N NaOH, after dissolution the volume was made up to the mark with 0.2 N NaOH (1000 µg/ml). Further dilution was made by pipetting 10 ml into 100 ml volumetric flasks to acquire 100 µg/ml solution made up with 0.2 N NaOH. Further dilution was made by pipetting 1, 2, 3, 4 and 5 ml into 25 ml volumetric flasks to acquire 4, 8, 12, 16 and 20 µg/ml solution made up with 0.2 N NaOH. The absorbance measurements of these solutions were carried out against 0.2 N NaOH as blank at 252 nm. A calibration curve of Celecoxib was plotted.

Standard curve of Celecoxib in Simulated Gastric Fluid (without Enzyme):

50 mg of Celecoxib was weighed accurately and transferred into 50 ml volumetric flask and dissolved in 3 ml of methanol, after dissolution the volume was made up to the mark with SGF (without enzyme) (1000 µg/ml). Further dilution was made by pipetting 10 ml into 100 ml volumetric flasks to acquire 100 µg/ml solution made up with SGF (without enzyme). Further dilution was made by pipetting 1, 2, 3, 4 and 5 ml into 25 ml volumetric flasks to acquire 4, 8, 12, 16 and 20 µg/ml solution made up with SGF (without enzyme). The absorbance measurements of these solutions were carried out against SGF (without enzyme) as blank at 249 nm. A calibration curve of Celecoxib was plotted.

7.1.5. Determination of percentage purity of drug: *(Fabián Teixeira Primo., et al., 2005)*

Percentage purity of Celecoxib in 0.2 N Sodium Hydroxide:

50 mg of Celecoxib was weighed accurately and transferred into 50 ml volumetric flask and dissolved in 0.2 N NaOH, after dissolution the volume was made up to the mark with 0.2 N NaOH (1000 µg/ml). Further dilution was made by pipetting 10 ml into 100 ml volumetric flasks to acquire 100 µg/ml solution made up with 0.2 N NaOH. Further dilution was made by pipetting 3 ml into 25 ml volumetric flasks to acquire 12 µg/ ml solution made up with 0.2 N NaOH.

Percentage purity of Celecoxib in Simulated Gastric Fluid (without Enzyme):

50 mg of Celecoxib was weighed accurately and transferred into 50 ml

volumetric flask and dissolved in 3ml of methanol, after dissolution the volume was made up to the mark with Simulated Gastric Fluid (without Enzyme) (1000 µg/ml). Further dilution was made by pipetting 10 ml into 100 ml volumetric flasks to acquire 100 µg/ml solution made up with Simulated Gastric Fluid (without Enzyme). Further dilution was made by pipetting 3 ml into 25 ml volumetric flasks to acquire 12 µg/ ml solution made up with Simulated Gastric Fluid (without Enzyme).

7.1.6. Determination of drug-polymer compatibility (*Patil S.V., et al., 2009)*

Drug polymers studies holds great importance in designing a formulation. In drug formulation it is essential to evaluate the possible interactions between the active principle and the polymers, as the choice of the polymers should be performed in relation to the drug delivery, to their compatibility with the same drug and to the stability of the final product. The proper design and formulation of a dosage form requires consideration of the physical, chemical and biological characteristics of all drug substances and excipients to be used in the fabricating the product. Each polymer used in the formulations was blended with the drug levels that are realistic with respect to the final dosage form.

A] Fourier transforms infra-red (FTIR) spectroscopy *(Patil S.V., et al., 2009; IP, 2007; http://en.wikipedia.org/wiki/Fourier_transform_infrared_spectroscopy)*

FTIR study was carried out to check compatibility of drug with polymers. Infrared spectrum of Celecoxib was determined on Fourier transform Infrared Spectrophotometer using KBr dispersion method. The base line correction was done

using dried potassium bromide. Then the spectrum of dried mixture of drug and potassium bromide was run followed by drug with various polymers by using FTIR spectrophotometer. The absorption maximums in spectrum obtained with the substance being examined correspond in position and relative intensity to those in the reference spectrum.

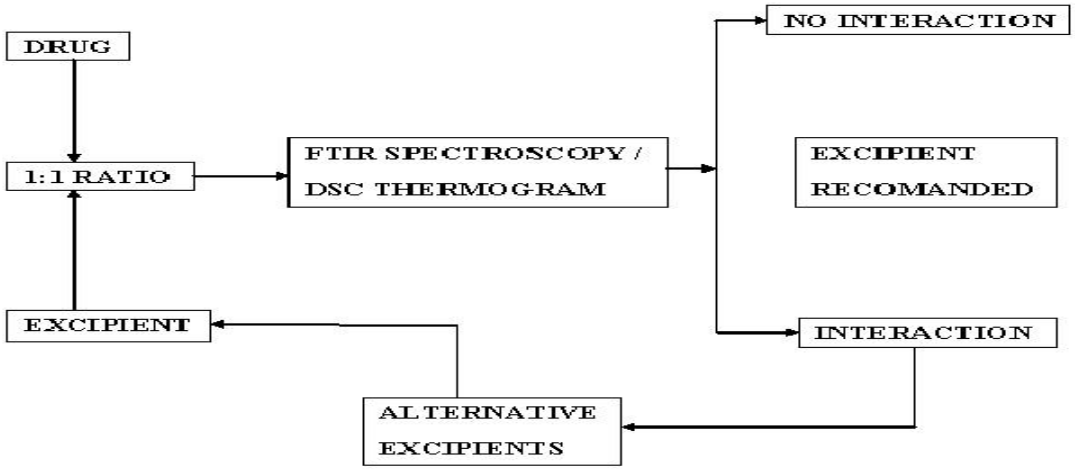

Figure 7.1 Compatibility studies

B] Differential Scanning Calorimetry (DSC) *(Patil S.V., et al., 2009; Aulton M. E., 2002; http://en.wikipedia.org/wiki/Differential_scanning_calorimetry)*

Any possible drug polymer interaction can be studied by thermal analysis. The DSC study was performed on pure drug Celecoxib, Celecoxib with HPMC K15M, Celecoxib with Ethyl cellulose and Celecoxib with HPMC K15M and Ethyl cellulose. The mixture of drug with polymers to maximize the like hood of obscuring an interaction. Mixture should be examined under Nitrogen to eliminate oxidative and pyrolytic effect at a standard heating rate (10°C/minute) on DSC. Over a temperature range, which will encompass any thermal changes due to the mixture of drug with

polymers. Thermo grams of pure drug are used as a reference.

Appearance or disappearance of one or more peaks in thermo grams of drug with polymer are considered as an indication of interaction. 2 mg of sample were heated in a hermetically sealed aluminum pans in the temperature range of 50 to 250 ºC at heating rate of 10 ºC / min under nitrogen flow of 30 ml / min.

7.2 PREPARATION OF NON-EFFERVESCENT FLOATING MICROPARTICULATES: *(Satish Singh., et al., 2012)*

The non-effervescent floating microparticulates were prepared by solvent diffusion and evaporation method, by using a drug and polymers in different concentrations. The formulations were designated as F1, F2, F3, F4, F5, F6, F7, F8 and F9 respectively.

Table7.2: The compositions of formulations

Ingredients (gm)	**Formulations**								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Celecoxib	1	1	1	1	1	1	1	1	1
HPMC K15M	0.25	-	0.5	0.5	-	1	1	0.5	0.75
Ethyl cellulose	0.25	0.5	-	0.5	1	-	0.5	1	0.75

Solvent diffusion and evaporation method:

Microparticulates were prepared by using the technique in which polymers (HPMC K15M and Ethyl Cellulose) were dissolved in 15ml equimolar mixture of dimethyl formamide and dichloromethane and stirred for 5 minutes using magnetic stirrer

at 100 rpm. Drug was added into the polymer solution with continuous stirring for 5 minutes at 100 rpm. This solution was slowly poured into 100 ml light liquid paraffin containing 2.0% w/w Tween-80 and stirred using mechanical stirrer for 8 hours at 750 rpm. Finally developed microparticulates were filtered and washed with petroleum ether and dried at room temperature for 4-6 hours.

7.3 EVALUATION OF NON-EFFERVESCENT FLOATING MICROPARTICULATES:

A] Appearance:

The microparticulates were visually observed for physical appearance.

B] Percentage Yield: *(Venkatesan P et al., 2011; Bindhu Madhavi., et al., 2011)*

The percentage yield was calculated from the ratio of filtered and dried microparticulates amount of each formulation to total solid material (non-volatile) content in the dispersed phase. The percentage yield of the prepared microparticulates was calculated by using the following formula.

$$\text{Percentage Yield} = \frac{\text{Weight of Microparticulates}}{\text{(Weight of Drug + Polymer taken)}} \times 100$$

Micromeritic Properties:

C] Bulk Density: *(USP, 2012)*

Accurately weighed quantity of floating microparticulates from each formula was lightly shaken to break any agglomerates formed and it was introduced in to a 10 ml measuring cylinder. The volume occupied was measured which gave bulk volume. The bulk density of floating microparticulates was determined using the following formula.

Bulk density (g/mL) = Weight of microparticulates taken / Bulk volume

D] Tapped Density: Yasunori *et al* (2003)

Accurately weighed quantity of floating microparticulates was transferred into a 10 ml measuring cylinder. After observing the initial volume of floating microsphere, carry out 500 taps from 3mm of height. Change in volume was noted and the tapped density was calculated according to the formula.

Tapped density = Weight of microparticulates taken / Tapped volume

E] Carr's Compressibility Index: *(USP, 2012)*

It is a simple index that can be determined on small quantities of powder. In theory, the less compressible a material the more flowable it is. The compressibility indices of the powder blends was determined using following formula,

$$\text{Carr's Compressibility Index} = \frac{\text{Tapped Density - Bulk density}}{\text{Tapped Density}} \times 100$$

F] Hausner's Ratio: *(USP, 2012)*

Hausner's ratio is the ratio between tapped density and bulk density. Hausner's ratio less than 1.25 indicates good flow properties while Hausner's ratio greater than 1.25 shows poor flow of granules.

Hausner's Ratio = Tapped Density / Bulk Density

G] Angle of Repose: *(USP, 2012)*

The dried microparticulates were allowed to fall freely through a funnel fixed at height of 3 cm on a horizontal surface and the angle of repose (θ) was measured.

$$\theta = \tan^{-1}(h/r)$$

Where h is the height of the heap, r is the radius.

Table 7.3 Relationship between Flow property, Angle of Repose, Carr's Index and Hausner's Ratio

Flow Property	Angle of Repose (°C)	Carr's Compressibility Index (%)	Hausner's Ratio
Excellent	25–30	10	1.00–1.11
Good	31–35	11–15	1.12–1.18
Fair—aid not needed	36–40	16–20	1.19–1.25
Passable—may hang up	41–45	21–25	1.26–1.34
Poor—must agitate, vibrate	46–55	26–31	1.35–1.45
Very poor	56–65	32–37	1.46–1.59
Very, very poor	>66	>38	>1.60

H] Particle size distribution: *(Sathish Singh, et al., 2012)*

Particle size distribution of microparticulates was determined by Malvern Particle size analyzer (Master Seizer 2000) by solvent dispersion method. Approximately 1 g of microparticulates was used for determination of microparticulates.

I] Scanning electron microscopy (SEM) *(USP, 2012)*

The surface morphology (roundness, smoothness and formation of aggregate and the size of microparticulates formulation were studied by Scanning electron microscopy. The solid sample of microparticulates were dispersed in water for SEM analysis was coated with a thin layer of platinum or gold using the PVD process at a 30MA current from the distance of 50nm. Photographs were taken within the range of 50-500 magnification.

J] Loss on Drying: *(Sathish Singh, et al., 2012)*

Loss on drying is the loss of weight expressed as percentage w/w resulting from water and volatile matter of any kind that can be driven off under specified condition. The accurately weighed 0.5 gm of microparticulates was transferred instoppered-glass shallow weighing bottle and accurately weighed the bottle. The bottle was transferred in oven and microparticulates were dried at 105°C for 3 hours. The bottle was removed from oven and reweighed; loss on drying was calculated by following equation.

$$\text{Loss on Drying} = \frac{\text{[Initial Weight taken - Final Weight after drying]}}{\text{Initial Weight taken}} \times 100$$

7.3.1 Buoyancy Test: *(Sathish Singh, et al., 2012)*

Weighed amount of microparticulates were sprinkled over the surface of 900 ml stimulated gastric fluid USP dissolution apparatus (Type II). The medium was agitated with a paddle rotating at 50 rpm for 12 hours. The floating and the settled portions of microparticulates were recovered separately. The microparticulates were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the microparticulates that remained floating and the total mass of the microparticulates.

$$\% \text{ Buoyancy} = \frac{\text{Weight of the floating microparticulates} \times 100}{\text{(Weight of the floating microparticulates + settled microparticulates)}}$$

Figure 7.2 Top view showing floating microparticulates in Buoyancy test

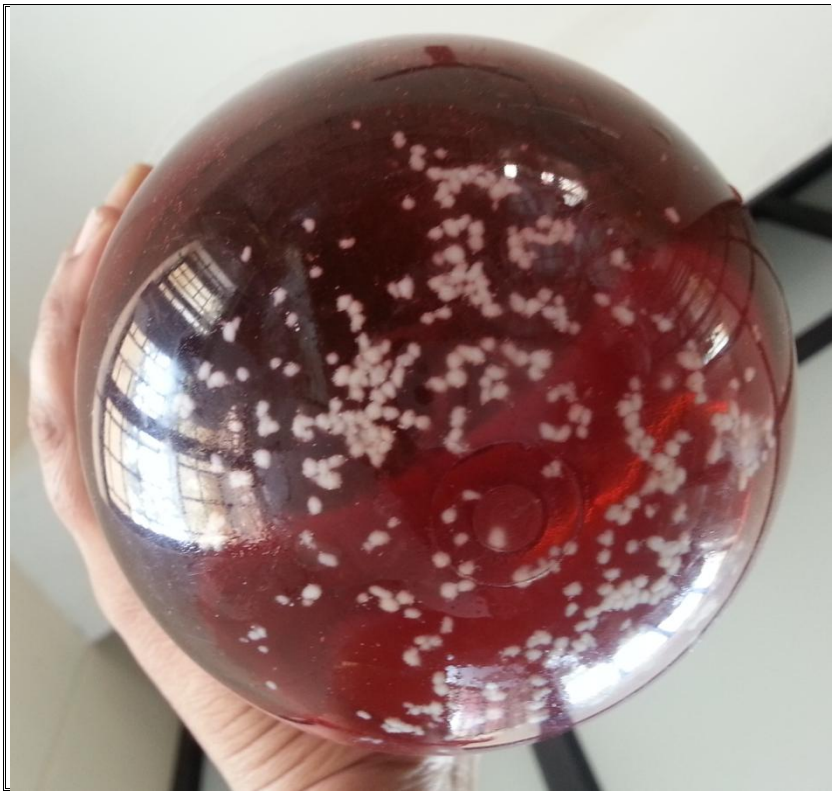

Figure 7.3 Bottom view showing settled microparticulates in Buoyancy test

Figure 7.4 Floating and settled microparticulates in Buoyancy test

Table 7.4 Parameters for Buoyancy Test

S. No.	Parameter	Specification
1	Apparatus	USP type II apparatus (Paddle type)
2	Temperature	37 ± 0.5° C
3	Initial volume	900ml
4	Speed	50 rpm
5	Drawn volume	10 ml
6	Running time	12 hours in Simulated gastric fluid
7	Medium replacement	at every 1 hour interval

7.3.2 Entrapment Efficiency: *(Sathish Singh, et al., 2012)*

Crushed microparticulates (equivalent to 100 mg of active substance) were dissolved in methanol to dissolved the drug completely and transferred slowly into 900 ml in SGF media (without enzyme) and stirred for 20 minutes. The solution was then filtered and 10 ml of the solution was made upto 100ml with SGF media (without enzyme). The samples were analyzed at λ max 249 nm against SGF as a blank using UV visible spectrophotometer.

7.3.3 *In-vitro* Drug release studies: *(Sathish Singh, et al., 2012)*

Dissolution test was performed by using USP tablet dissolution apparatus Type I (Veego scientific VDA-8DR). The dissolution medium used was 900 ml of SGF without enzyme. The weighed quantity of microparticulates equivalent to 100 mg of active substance filled into capsule cell and kept into dissolution medium which was set at 37 ± 0.5 ℃ and stirred at 50 rpm. To keep the microparticulates in dissolution medium

baskets of 100 meshes were used instead of paddles. 10 ml samples were withdrawn at predetermined time intervals of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hours and same volume of medium was replaced. The withdrawn sample were diluted to 100 ml with SGF without enzyme and analyzed in UV visible spectrophotometer at λ max 249 nm.

Table 7.5 Parameters for *in-vitro* drug release

S. No.	**Parameter**	**Specification**
1	Apparatus	USP type I apparatus (Basket type)
2	Temperature	37 ± 0.5° C
3	Initial volume	900ml
4	Speed	50 rpm
5	Drawn volume	10 ml
6	Running time	12 hours in SGF without enzyme
7	Medium replacement	at every 1 hour interval

7.3.4 Kinetics of *in-vitro* drug release: *(Amitava G.,et.al., 2009: Harris M.S.,et al.,2006)*

To study the release kinetics of *in-vitro* drug release, data was applied to kinetic models such as Zero order, First order, Higuchi and Korsmeyer- Peppas.

- **Zero order model:**

  $$\mathbf{Q_t = Q_0 + K_0 t}$$

  Q_t is the amount of drug dissolved in time *t*

  Q_0 is the initial amount of drug in the solution (most times, $Q_0 = 0$)

  K_0 is the zero order release constant expressed in units of concentration/time.

- **First order model:**

  $\log C = \log C_0 - Kt / 2.303$

  C_0 is the initial concentration of drug

  t is the time

  K is first order rate constant expressed in units of $time^{-1}$

- **Higuchi model:**

  $f_t = Q = K_H \times t^{0.5}$

  K_H is the Higuchi dissolution constant

  Q is the amount of drug released in time t

- **Korsmeyer-peppas model:**

  $Mt / M_0 = K t^n$

  Mt / M_0 is a fraction of drug released at time t

  k is the release rate constant

  n is the release exponent

Table 7.6 Diffusion exponent and solute release mechanism

Diffusion exponent (n)	Overall solute diffusion mechanism
< 0.5	Quasi-Fickian diffusion
0.5	Fickian diffusion
0.5 < n < 1.0	Anomalous (non-Fickian) diffusion
1.0	Case-II transport
> 1.0	Super case-II transport

The value of n give an indication of the release mechanism; when n=1, the release rate is independent of time (Zero order) (Case II transport), n=0.5 for fickian diffusion and when $0.5<n>1.0$, diffusion and non fickian transport are implicated. Lastly, when $n>1.0$ super case II transport is apparent. The interpretation release profile of all formulation data was based on the value of the resulting regression coefficient.

7.3.5 *Ex-vivo* permeation studies: *(Sathish Singh, et al., 2012)*

Goat stomach of scarified goat collected from slaughter house. Stomach was cleaned with simple saline. The non effervescent floating microparticulates equivalent to 100 mg of active substance was placed in the cylindrical cup which was connected to shaft and membrane tied with the end of cylindrical cup. The cup of tied membrane was immersed in USP dissolution jar containing 900 ml SGF at 37 ± 2ºC and stirred at 100 rpm. 10 ml samples were withdrawn at predetermined time intervals of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hours and same volume of medium was replaced with fresh medium. The withdrawn sample were diluted to 100 ml with SGF without enzyme and analyzed in UV visible spectrophotometer at λ max 249 nm.

Table 7.7 Parameters for *ex-vivo* Permeation studies

S. No.	Parameter	Specification
1	Apparatus	USP dissolution apparatus
2	Temperature	37 ± 2° C
3	Initial volume	900ml
4	Speed	100 rpm
5	Drawn volume	10 ml
6	Running time	12 hours in SGF
7	Medium replacement	at every 1 hour interval

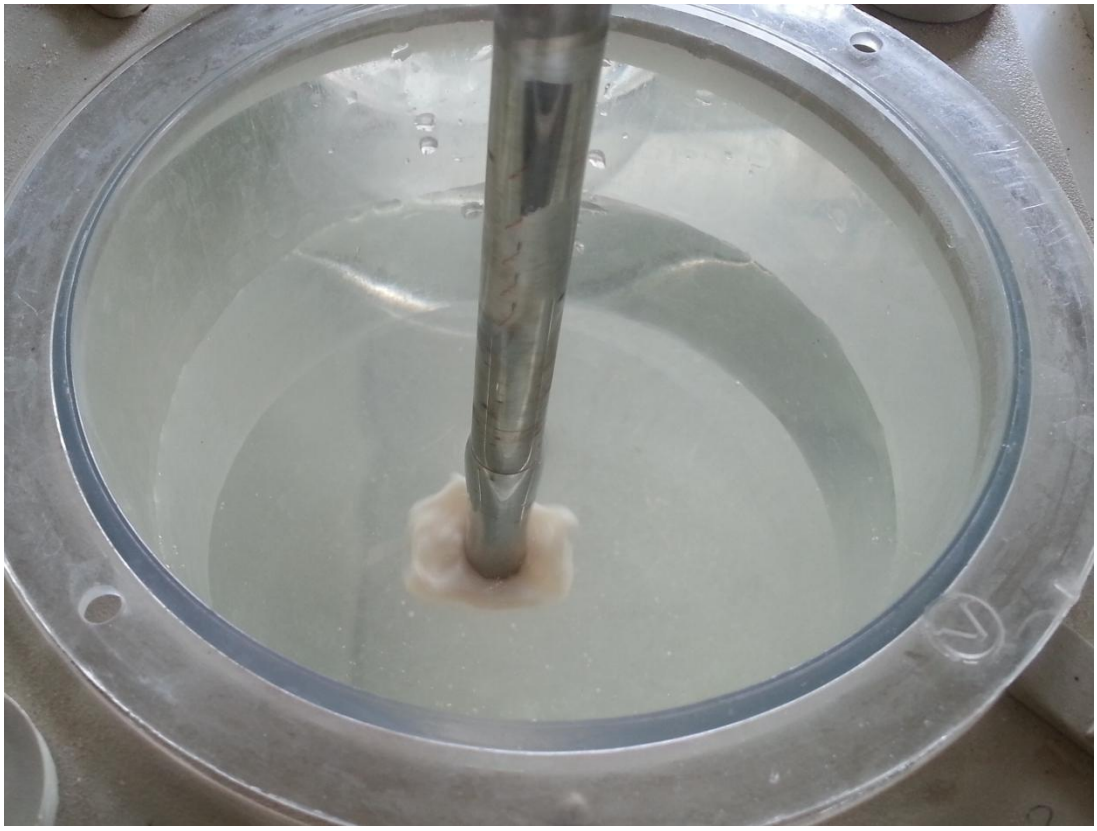

Figure 7.5 *Ex-vivo* permeation study using goat stomach membrane

7.4 Stability Studies: *(Sathish Singh, et al., 2012)*

The purpose of stability testing was to obtain a stable product which assures its safety. Floating microparticulates (equivalent to 100 mg of active substance) was filled into capsule shell. Floating microparticulates were tested for three months stability studies at room temperature. *In-vitro* drug released and buoyancy parameters were analyzed at the time interval of one month.

RESULTS AND DISCUSSION

8. RESULTS AND DISCUSSION

PREFORMULATION STUDIES

8.1. Identification of drug

A] By FTIR spectroscopy

The FTIR spectrum of Celecoxib was shown in Figure 8.1 and the interpretations of FTIR frequencies were represented in Table 8.1

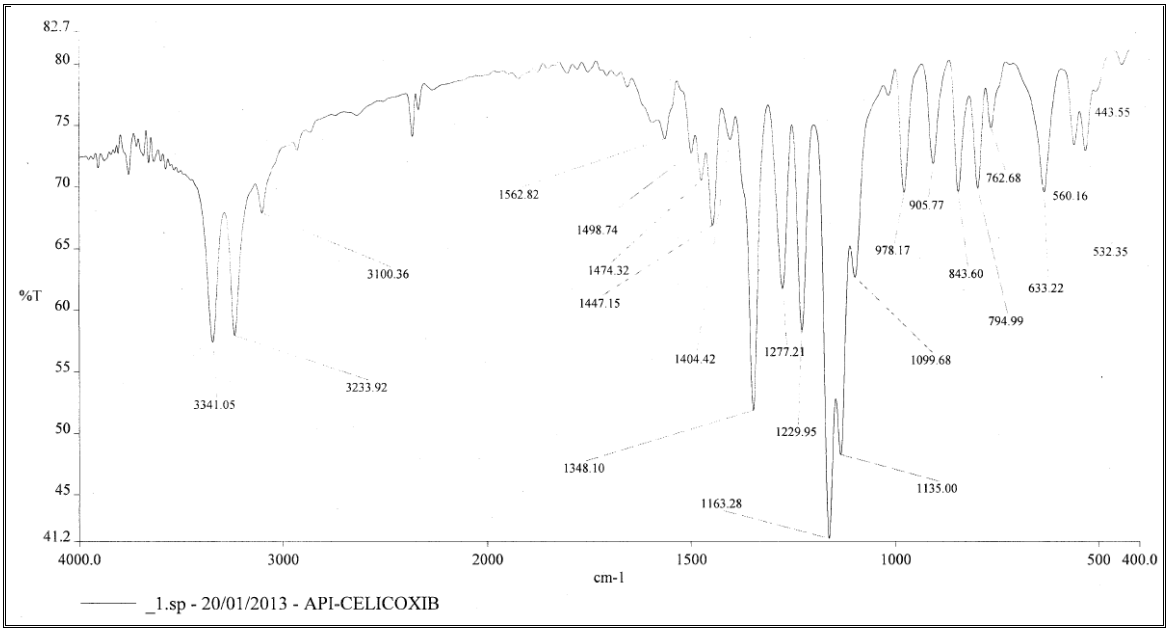

Figure 8.1: FTIR spectrum of Celecoxib

Table 8.1 Characteristic frequencies in FTIR spectrum of Celecoxib

Wave No. (cm^{-1})	Observed Wave No's	Inference
780 – 820 cm^{-1}	794.99	Aromatic CH stretching
1150 - 1350 cm^{-1}	1135.00, 1163.28, 1229.95, 1277.21, 1348.10	S=O stretching (Sulfonamide group)
1550 - 1600 cm^{-1}	1562.82	H stretching
3200 - 3500 cm^{-1}	3233.92, 3341.05	NH_2 stretching

Interpretation of FTIR Spectrum

Major functional groups like NH_2 stretching, H stretching, Aromatic CH stretching, and S=O stretching (Sulfonamide group) were present in Celecoxib showed characteristic peaks in FTIR spectrum. The major peaks were identical to functional group of Celecoxib. Hence, the sample was confirmed as Celecoxib.

B] By Melting point:

Melting point values of Celecoxib drug was found to be in range of 160°C to 164°C, which was represented in Table 8.2. The observed melting point for Celecoxib was 161.67 ± 0.58 °C, which meets the specification limit.

Table 8.2 Melting point of Celecoxib

S.No.	Melting Point	Average	Standard Deviation	Range*
1	162°C	161.67	0.58	161.67 ± 0.58 °C
2	162°C			
3	161°C			

*Range is expressed as Mean ± S.D., n = 3.

8.2. Physicochemical parameters

A] Organoleptic properties

Table 8.3 Organoleptic properties of Celecoxib

Properties	Specification	Observation
Color	White or almost white color	White color
Nature	Amorphous or crystalline powder	Amorphous powder
Odour	NA	Odourless

B] Solubility study

Solubility of Celecoxib in different solvents was represented in Table 8.4.

Table 8.4 Solubility profile of Celecoxib

S. No.	Solvent	Parts of solvent required per part of solute	Inference
1	Water	10,000	Practically Insoluble
2	Methanol	10	Freely Soluble
3	Ethanol (95%)	20	Soluble
4	0.1N Hydrochloric Acid	10,000	Practically Insoluble
5	O.1N Sodium Hydroxide	7	Freely Soluble
6	Dimethyl formamide	7	Freely Soluble

From the above data the solubility of Celecoxib was confirmed in various polar and non polar solvents.

C] Loss on drying:

The percentage loss on drying of microparticulates after 3 hours was represented in Table 8.5.

Table 8.5 Loss on drying for Celecoxib

S.No.	Percentage LOD	Average	Standard Deviation	Range*
1	0.4044	0.436 %	0.028	0.436 ± 0.028 %
2	0.4563			
3	0.4481			

*Range is expressed as Mean ± S.D., n = 3

8.3. Determination of λ max

Determination of λ max for Celecoxib in 0.2N Sodium Hydroxide:

The absorption maximum for Celecoxib in 0.2N Sodium Hydroxide was found to be 252 nm and absorption maximum was represented in Figure 8.2.

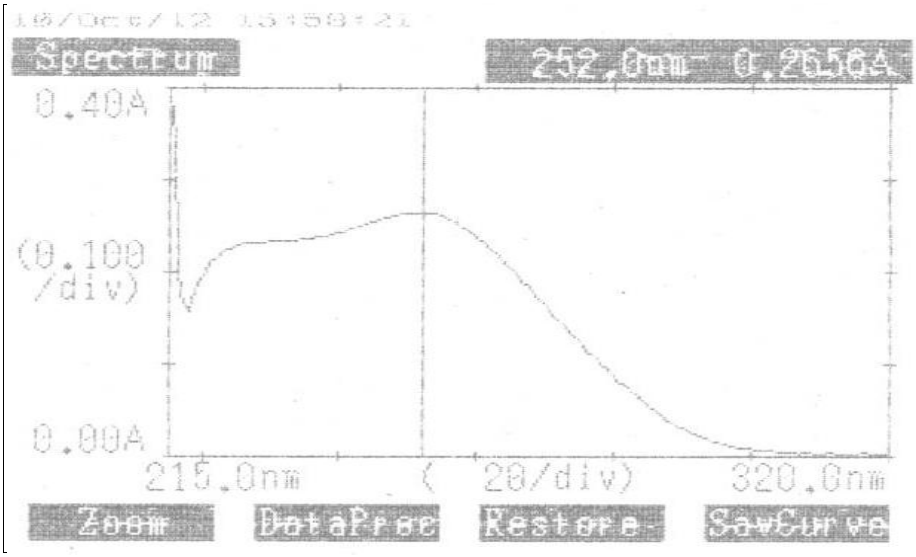

Figure 8.2 λ max observed for Celecoxib in 0.2N Sodium Hydroxide

Determination of λ max for Celecoxib in SGF (without enzyme):

The absorption maximum for Celecoxib in Simulated gastric fluid (without enzyme) was found to be 249 nm and absorption maximum was represented in Figure 8.3.

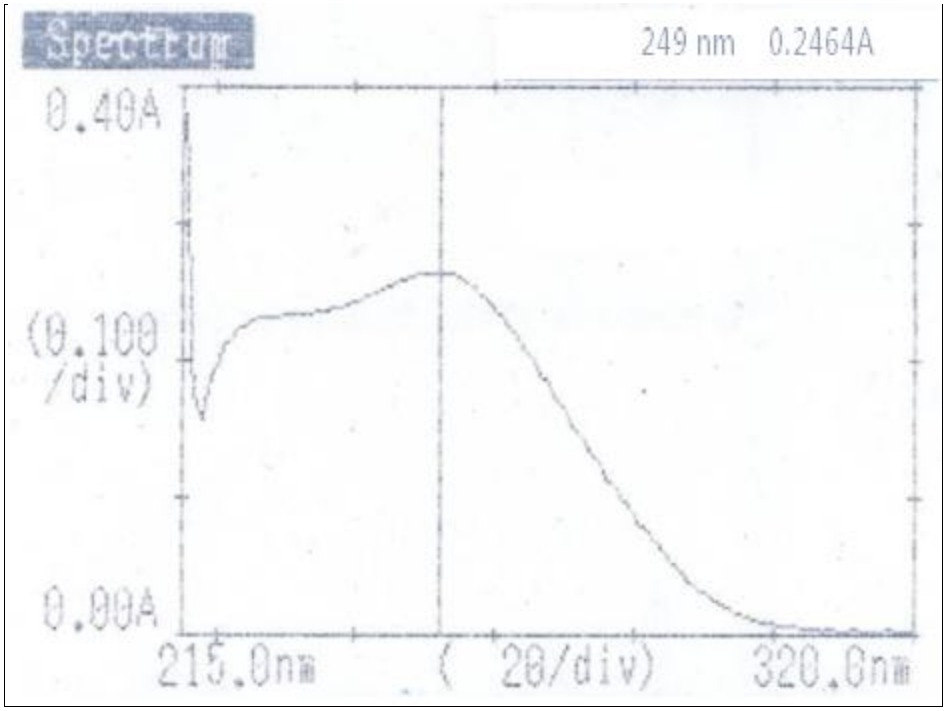

Figure 8.3 λ max observed for Celecoxib in SGF (without enzyme)

8.4 Development of standard curve of Celecoxib:

Development of standard curve of Celecoxib in 0.2 N Sodium Hydroxide

Absorbance obtained for various concentrations of Celecoxib in 0.2N Sodium Hydroxide were represented in Table.8.6.and Figure 8.4. The graph of absorbance Vs concentration for Celecoxib was found to be linear in the concentration range of 4 to 20 µg/ml. The calibration curve parameters were represented in Table: 8.7 and the drug obey Beer- Lambert's law.

Table: 8.6 Data of concentration Vs absorbance for Celecoxib in 0.2N Sodium hydroxide

S.No	Concentration (mcg/ml)	Absorbance at 252nm
1	4	0.145
2	8	0.301
3	12	0.453
4	16	0.594
5	20	0.740

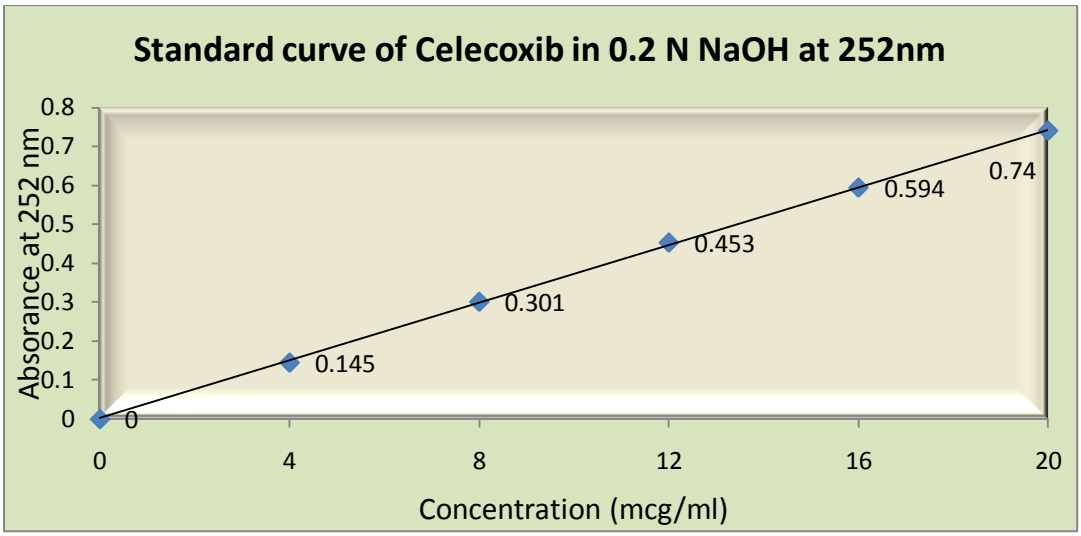

Figure 8.4 Standard graph of Celecoxib in 0.2N Sodium hydroxide

Table 8.7 Data for calibration curve Parameters of Celecoxib in 0.2N Sodium hydroxide

S. No	Parameters	Values
1	Correlation coefficient (r)	0.99989
2	Slope (m)	0.03714
3	Intercept (c)	0.00081

Development of standard curve of Celecoxib in SGF (without enzyme):

Absorbance obtained for various concentrations of Celecoxib in SGF (without enzyme) were represented in Table.8.8.and Figure 8.5. The graph of absorbance Vs concentration for Celecoxib was found to be linear in the concentration range of 4 to 20 µg/ml. The calibration curve parameters were represented in Table: 8.9 and the drug obey Beer- Lambert's law.

Table 8.8 Data of concentration Vs absorbance for Celecoxib in SGF (without enzyme)

S.No	Concentration (mcg/ml)	Absorbance at 249nm
1	4	0.127
2	8	0.236
3	12	0.353
4	16	0.475
5	20	0.604

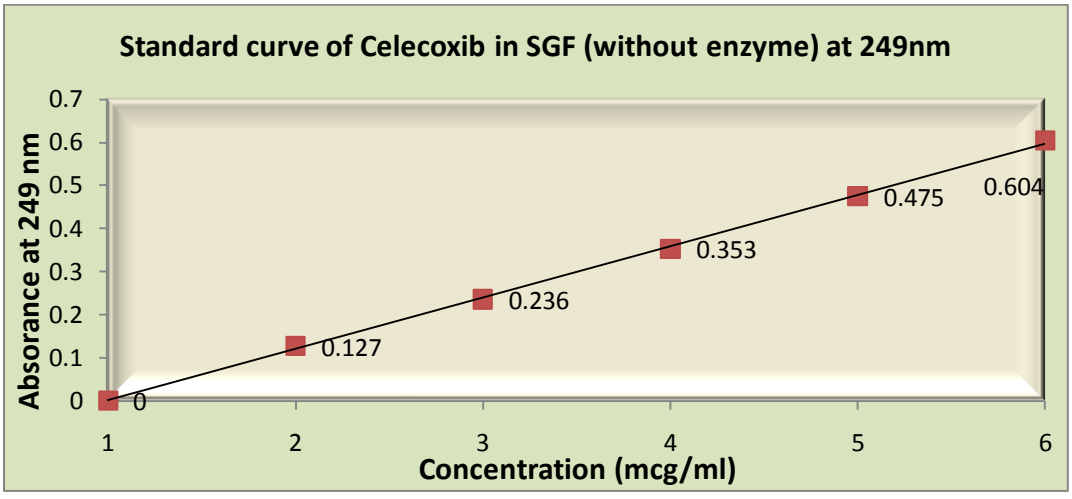

Figure 8.5 Standard graph of Celecoxib in SGF (without enzyme)

Table 8.9 Data for calibration curve Parameters of Celecoxib in SGF (without enzyme)

S. No	Parameters	Values
1	Correlation coefficient (r)	0.99971
2	Slope (m)	0.029864
3	Intercept (c)	0.00052

8.5 Determination of percentage purity of drug:

Percentage purity of Celecoxib in 0.2N Sodium hydroxide:

The percentage purity of Celecoxib was calculated by using calibration graph method and represented in Table 8.10

Table 8.10 Percentage purity of Celecoxib in 0.2N Sodium hydroxide

S.No.	Percentage Purity (% w/w)	Average (% w/w)
1	99.90 %	100.28 %
2	100.80 %	
3	100.17 %	

The reported percentage purity of Celecoxib in 0.2N Sodium hydroxide was 100.28%, which is within the USP specification range of 98.0% to 102.0%

Percentage purity of Celecoxib in SGF (without enzyme):

The percentage purity of Celecoxib was calculated by using calibration graph method and represented in Table 8.11

Table 8.11 Percentage purity of Celecoxib in SGF (without enzyme)

S.No.	Percentage Purity (% w/w)	Average (% w/w)
1	100.03	99.75 %
2	99.47	
3	99.75	

The reported percentage purity of Celecoxib in SGF (without enzyme) was 99.75%, which is within the USP specification range of 98.0% to 102.0%

8.6 Determination of drug-polymer compatibility:

A] By FTIR spectroscopy:

The FTIR spectrums of Celecoxib with polymers (HPMC K15M and Ethyl cellulose) used in formulation were showed in Figures 8.6 to 8.9, and their interpretations were represented in Table 8.12.

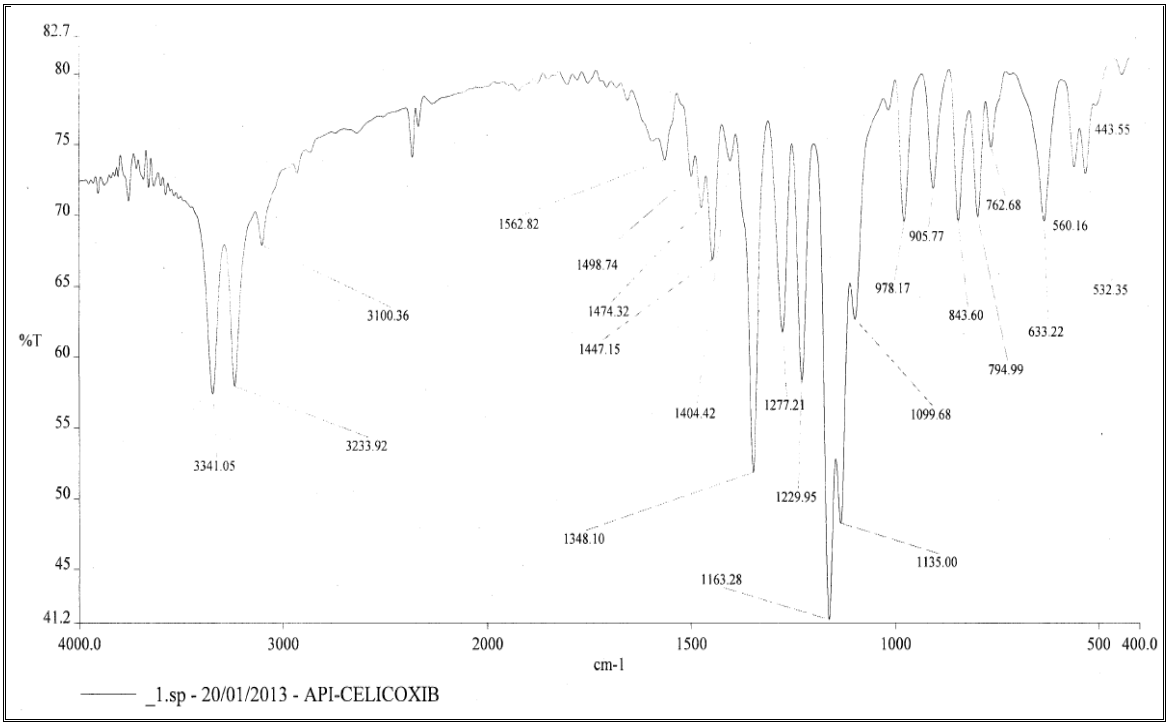

Figure 8.6 FTIR spectrum of Celecoxib

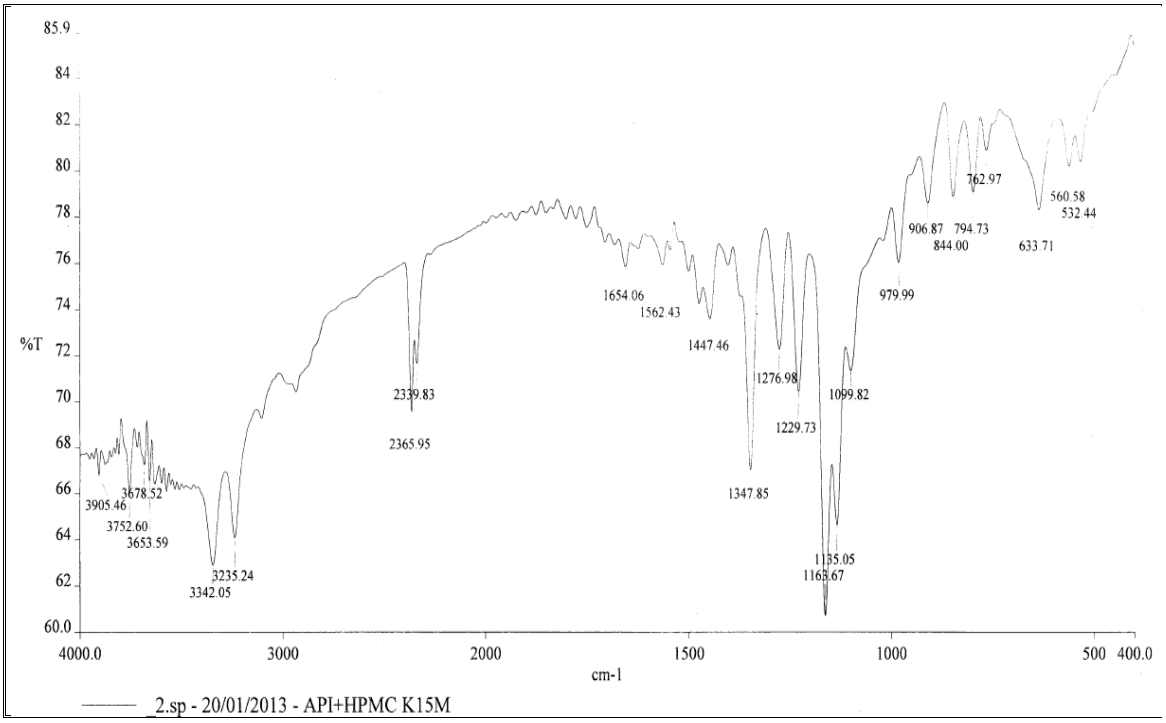

Figure 8.7 FTIR spectrum of Celecoxib with HPMC K15M

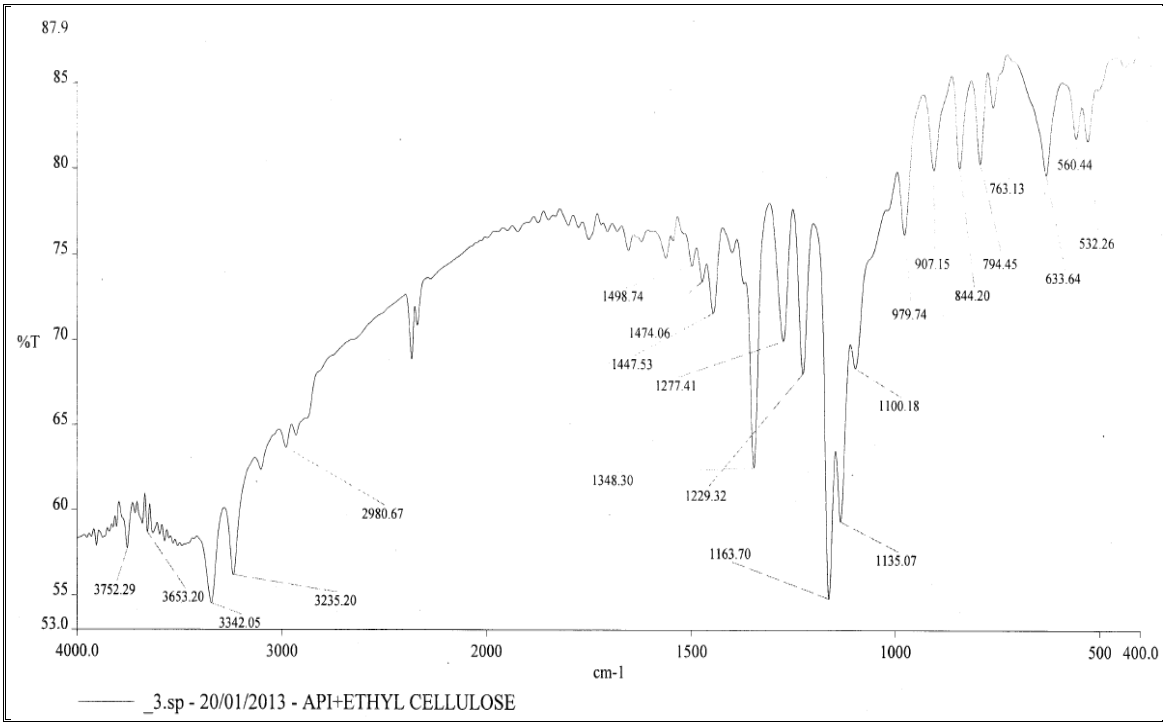

Figure 8.8 FTIR spectrum of Celecoxib with Ethyl cellulose

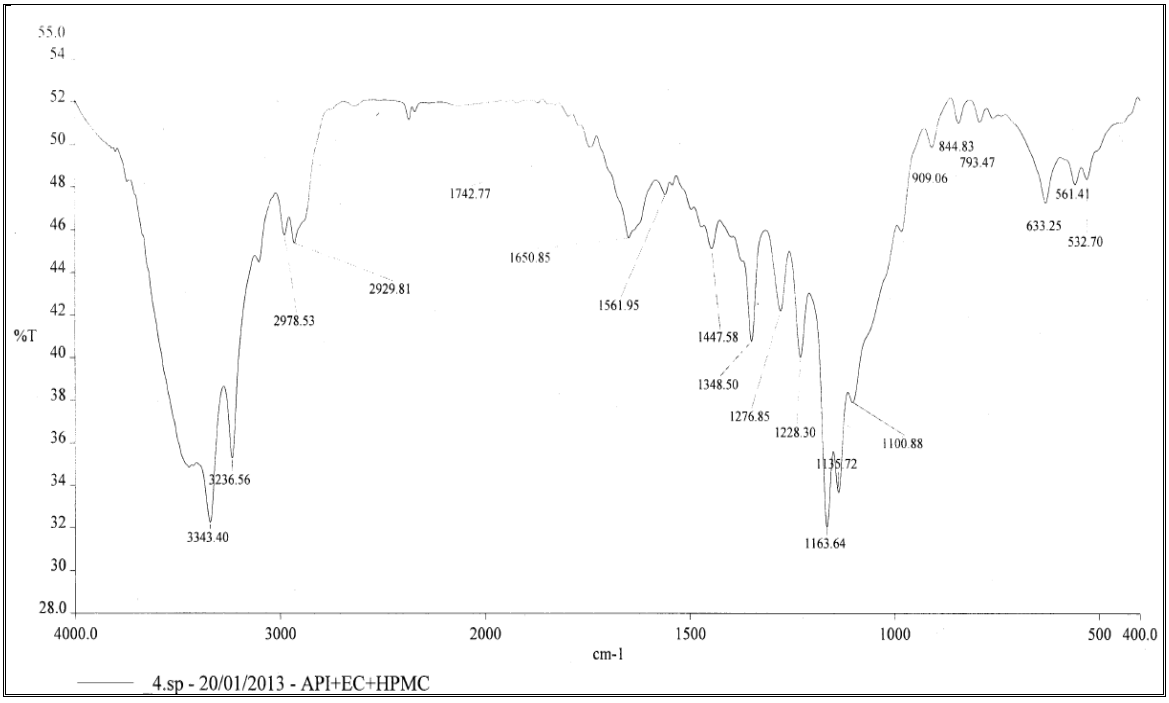

Figure 8.9 FTIR spectrum of Celecoxib with HPMC K15M and Ethyl cellulose

Table 8.12 Interpretation of FTIR Spectrum

Specification	Celecoxib drug	Celecoxib with HPMC K15M	Celecoxib with Ethyl Cellulose	Celecoxib with HPMC K15M and Ethyl Cellulose	Inference
Wave No. (cm^{-1})					
780 – 820 cm^{-1}	794.99	794.73	794.45	793.47	Aromatic CH stretching
1150-1350 cm^{-1}	1135.00, 1163.28, 1229.95, 1277.21, 1348.10	1135.05, 1163.67, 1229.73, 1276.98, 1347.85	1135.07, 1163.70, 1229.32, 1277.41, 1348.30	1135.72, 1163.64, 1228.30, 1276.85, 1348.50	S=O stretching (Sulfonamide group)
1550-1600 cm^{-1}	1562.82	1562.43	1561.74	1561.95	H stretching
3200-3500 cm^{-1}	3233.92, 3341.05	3235.24, 3342.05	3235.20, 3342.05	3236.56, 3343.40	NH_2 stretching

The major peaks observed in drug spectrum corresponds with peaks observed in drug with polymer spectrum. From the FTIR spectrums compared; it could indicate that there was no incompatibility between drug and polymer.

B] By DSC thermal analysis:

The DSC thermograms of Celecoxib with polymers (HPMC K15M and Ethyl cellulose) used in formulations were represented in Figures 8.10 to 8.13, and their comparison were represented in Table 8.13.

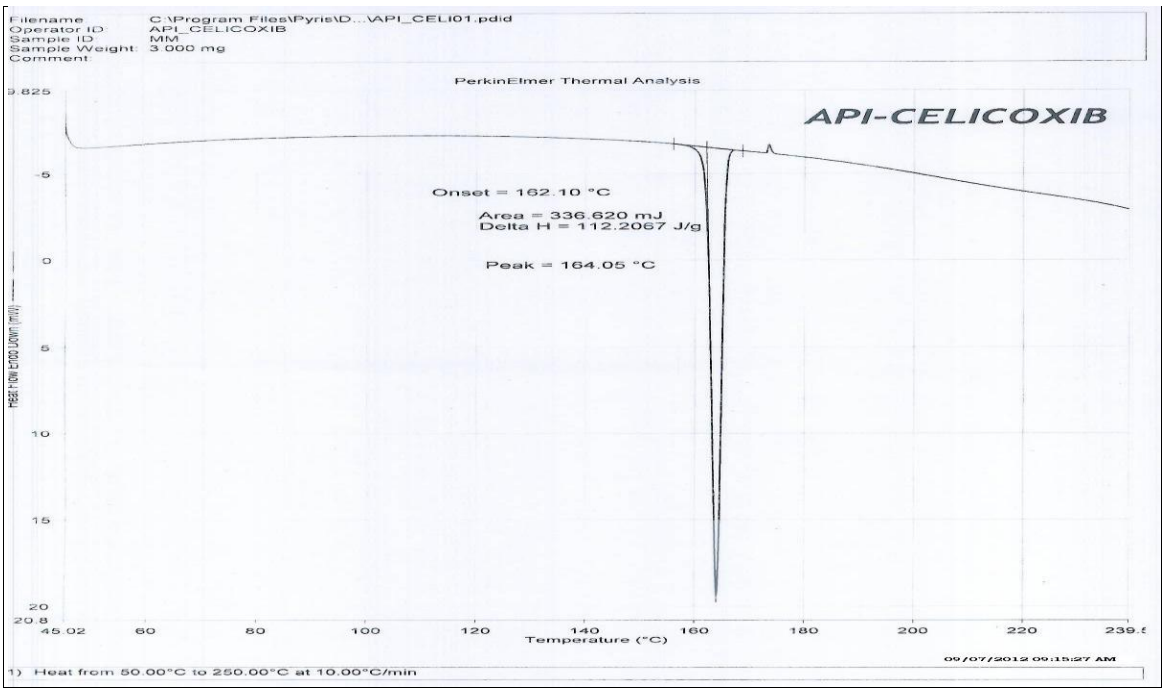

Figure 8.10 DSC thermogram of Celecoxib

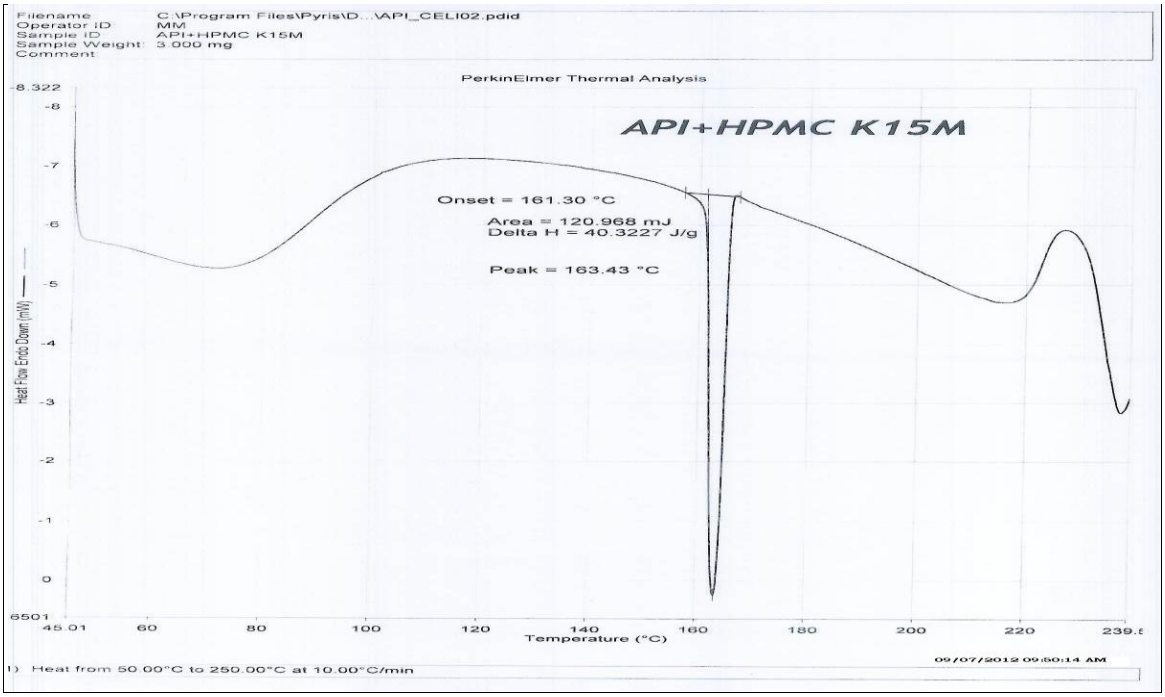

Figure 8.11 DSC thermogram of Celecoxib with HPMC K15M

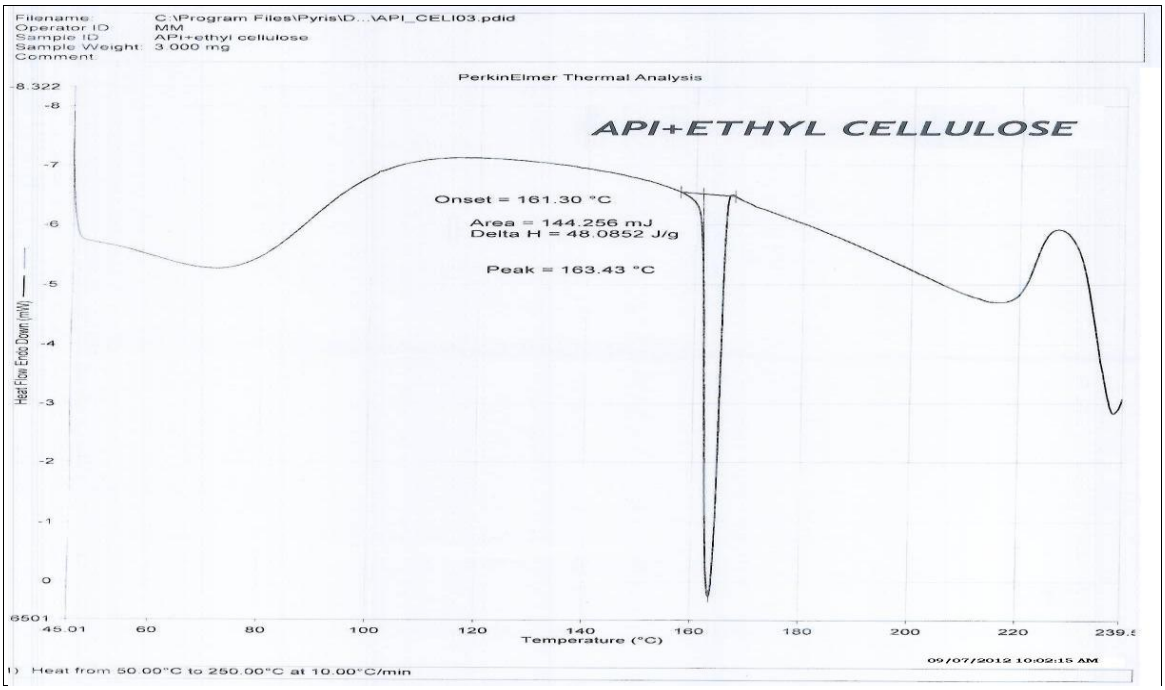

Figure 8.12 DSC thermogram of Celecoxib with Ethyl cellulose

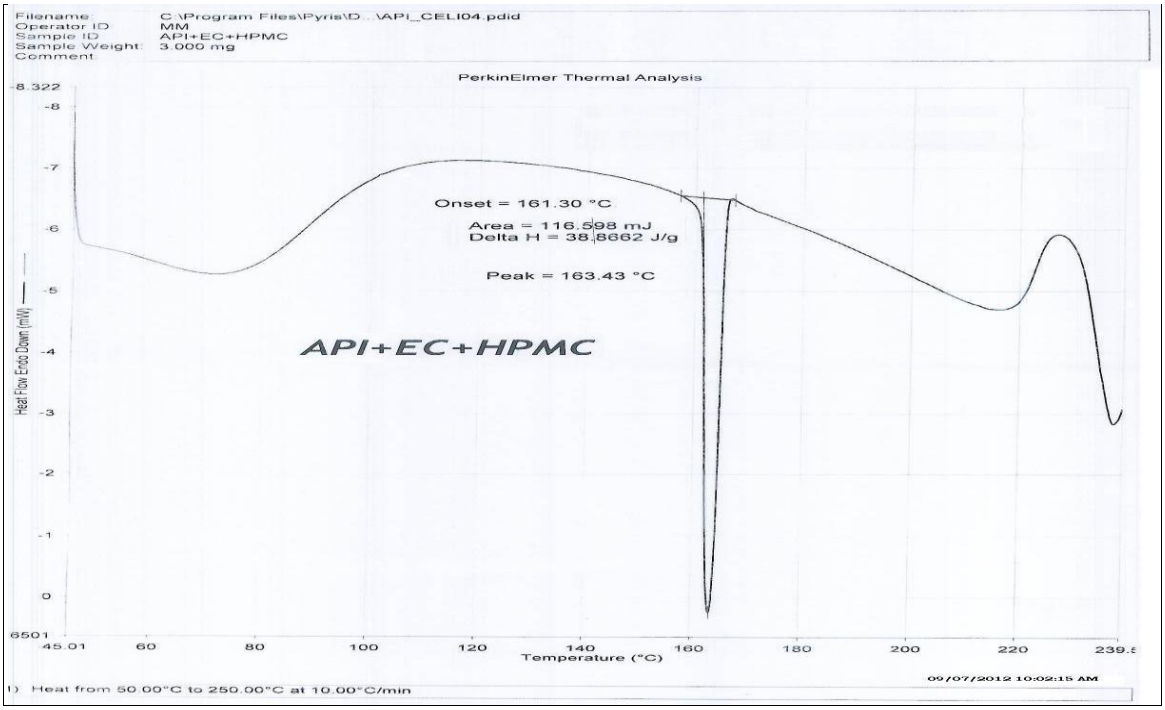

Figure 8.13 DSC thermogram of Celecoxib with HPMC K15M and Ethyl cellulose

Table 8.13: Comparison of DSC thermograms

DSC Thermogram	Onset Temperature (°C)	Peak Temperature (°C)
Celecoxib	162.10 ° C	164.05° C
Celecoxib with HPMC K15M	161.30° C	163.43° C
Celecoxib with Ethyl Cellulose	161.30° C	163.43° C
Celecoxib with HPMC K15M and Ethyl Cellulose	161.30° C	163.43° C

The drug and polymer interaction was studied by using DSC. Celecoxib exhibits a sharp endothermic peak which is corresponding with its melting point. The endothermic peak temperature of Celecoxib corresponds with the endothermic peak temperature of drug with polymer. No interaction was found between drug and polymers.

8.7 PREPARATION OF NON-EFFERVESCENT FLOATING MICROPARTICULATES:

Nine different formulations of non-effervescent floating microparticulates were prepared by solvent diffusion and evaporation method, by using a drug and with polymers in different concentrations. Polymers HPMC K15M and Ethyl cellulose were used in formulations. The formulations were designated as F1, F2, F3, F4, F5, F6, F7, F8 and F9 respectively. All the formulated microparticulates were taken for further evaluation.

8.8 EVALUATION OF NON-EFFERVESCENT FLOATING MICROPARTICULATES

A] Appearance:

The prepared microparticulates were visually observed, and found to be white crystalline mass.

B] Percentage Yield:

The percentage yield of microparticulates were in the range of 69.05 % to 83.82 %. Maximum yield was obtained in Formulation F5 (83.82 %), followed by F8 (82.53 %), F3 (79.77 %), F4 (79.38 %) and F9 (79.06 %). The percentage yield of the prepared microparticulates was represented in Table 8.14 and Figure 8.14.

Table 8.14 Percentage yield of microparticulates

Formulation No.	F1	F2	F3	F4	F5	F6	F7	F8	F9
Percentage Yield (% w/w)	77.15	69.05	79.77	79.38	83.82	76.73	70.98	82.53	79.06

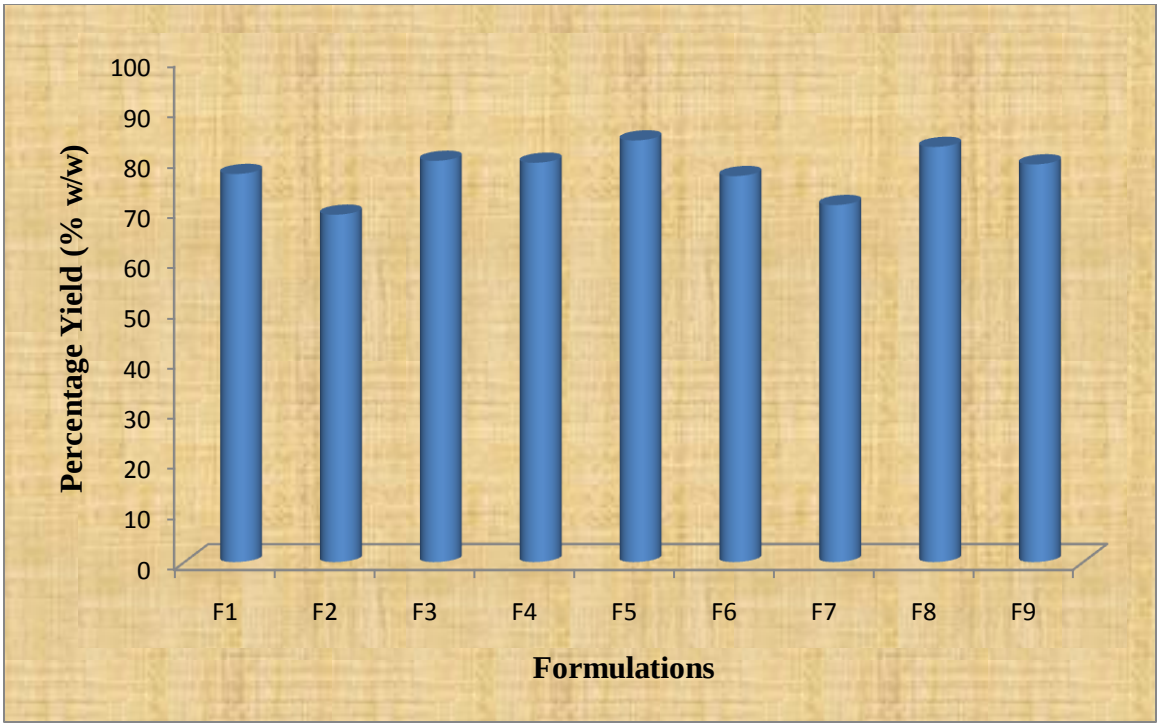

Figure 8.14 Percentage yield of microparticulates

8.8.1 MICROMERITIC PROPERTIES:

Bulk density, Tapped Density, Carr's Index, Hausner's ratio and Angle of repose:

The observed bulk density was in the range of 0.686 to 0.822 g/mL, Tapped density was in the range of 0.735 to 0.892 g/mL, Carr's index was in the range of 6.53 to 7.91 %, Hausner's ration was in the range of 1.07 to 1.09, and angle of repose was in the range of 21.18 to 24.09 ℃. From the above data, it is found that all the formulations were having excellent flow properties. Bulk density, Tapped density, Carr's compressibility index, Hausner's ratio and Angle of repose of non effervescent floating microparticulates were represented in Table 8.15 and Figure 8.15 to 8.18.

Table 8.15 Micromeritic properties of microparticulates

Formulation No.	Bulk Density (g/mL)*	Tapped Density (g/mL)*	Carr's Compressibility Index (%)	Hausner's Ratio	Angle of Repose (°C)*
F1	0.822 ± 0.022	0.892 ± 0.026	7.91	1.09	24.09 ± 0.34
F2	0.803 ± 0.012	0.868 ± 0.016	7.51	1.08	23.99 ± 0.88
F3	0.799 ± 0.010	0.866 ± 0.011	7.69	1.08	22.86 ± 0.91
F4	0.787 ± 0.012	0.851 ± 0.016	7.51	1.08	22.55 ± 0.90
F5	0.686 ± 0.007	0.735 ± 0.008	6.53	1.07	22.39 ± 0.90
F6	0.742 ± 0.059	0.800 ± 0.068	7.17	1.08	21.18 ± 0.67
F7	0.711 ± 0.038	0.763 ± 0.044	6.69	1.07	21.33 ± 0.41
F8	0.782 ± 0.021	0.844 ± 0.026	7.33	1.08	22.77 ± 0.56
F9	0.817 ± 0.018	0.885 ± 0.020	7.69	1.08	21.80 ± 0.39

* The values were expressed as Mean ± S.D., n = 3.

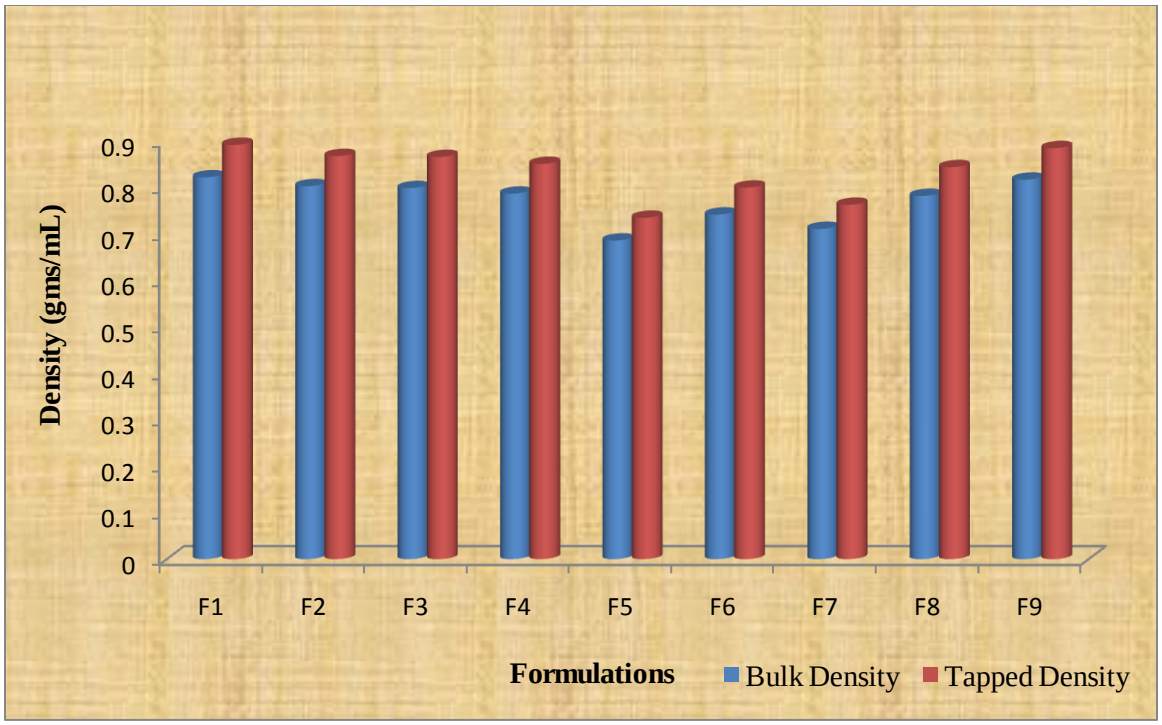

Figure 8.15 Bulk density and Tapped Density of microparticulates

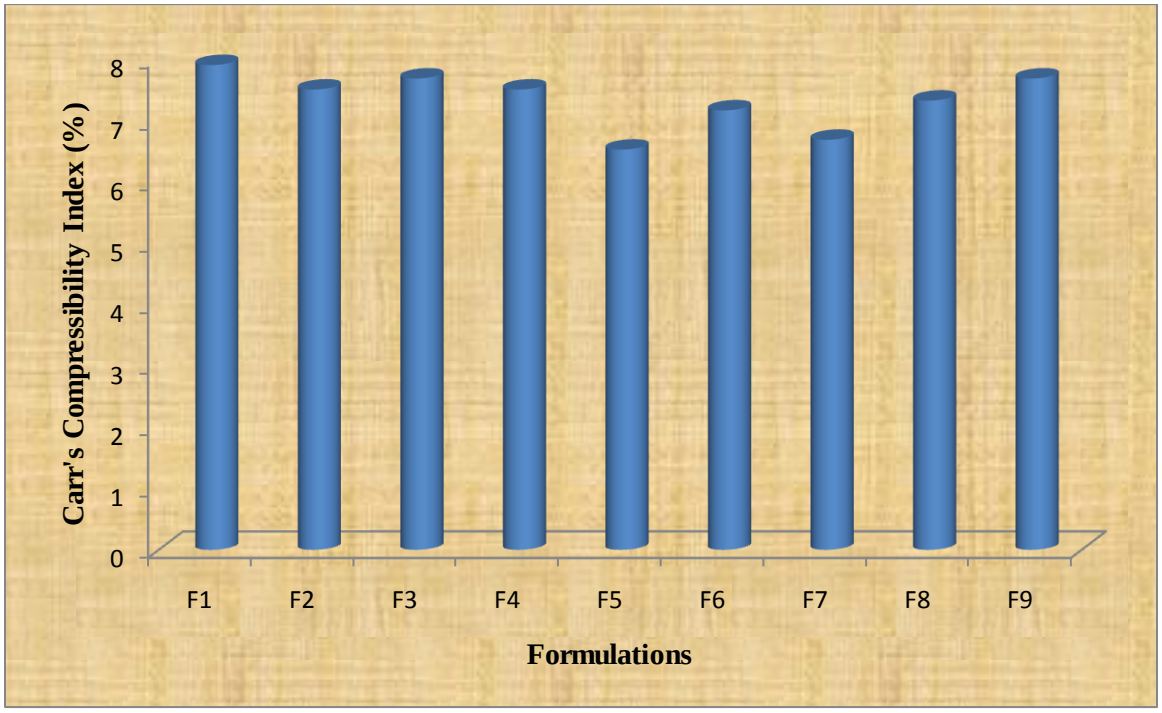

Figure 8.16 Carr's Compressibility Index of microparticulates

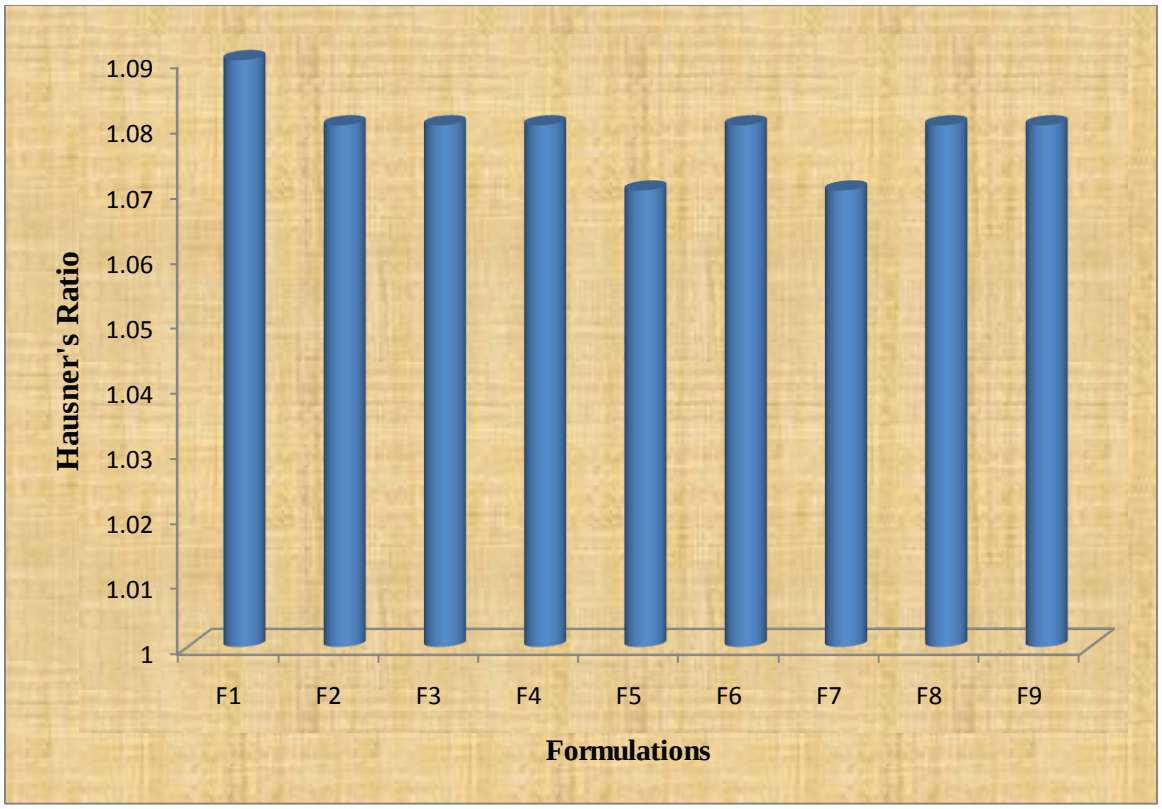

Figure 8.17 Hausner's Ratio of microparticulates

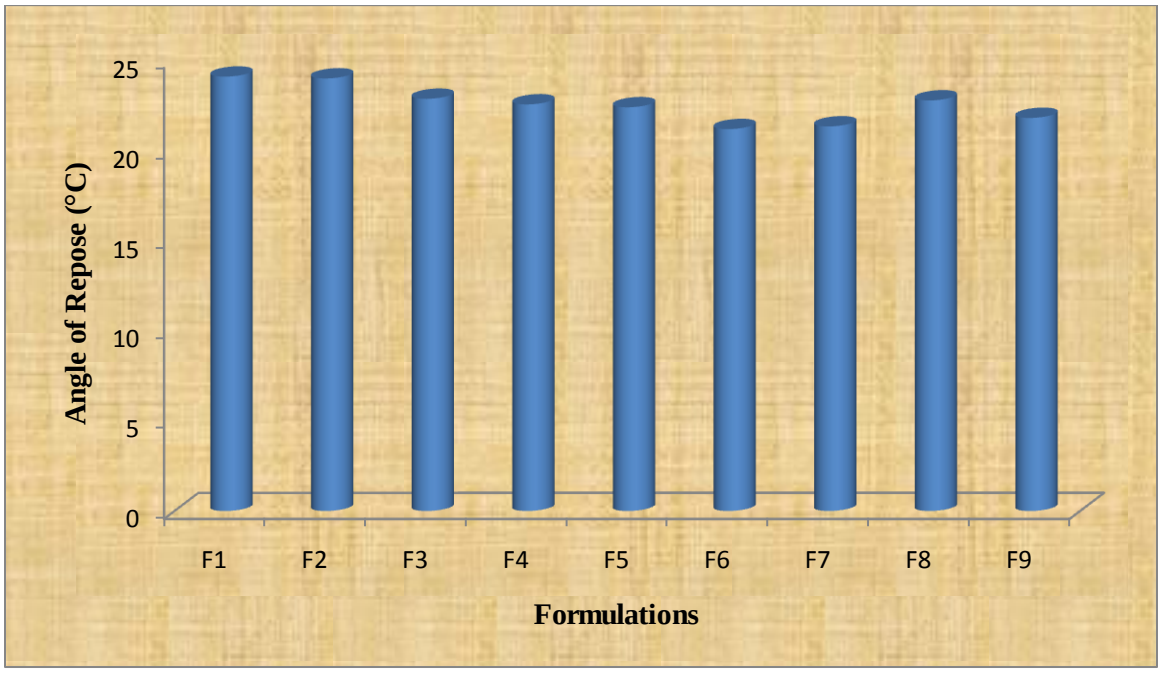

Figure 8.18 Angle of Repose of microparticulates

8.8.2 Particle size distribution:

Particle size distribution of microparticulates was determined using Malvern Particle size analyzer (Master Seizer 2000) by solvent dispersion method. The observed particle size of non effervescent floating microparticulates of formulation F5 was found to be 146.01 µm. The results obtained were represented in Table 8.16 and Figure 8.19.

Table 8.16 Particle size distribution of microparticulates

Formulation No.	Particle Size (µm)
F5	146.01 µm

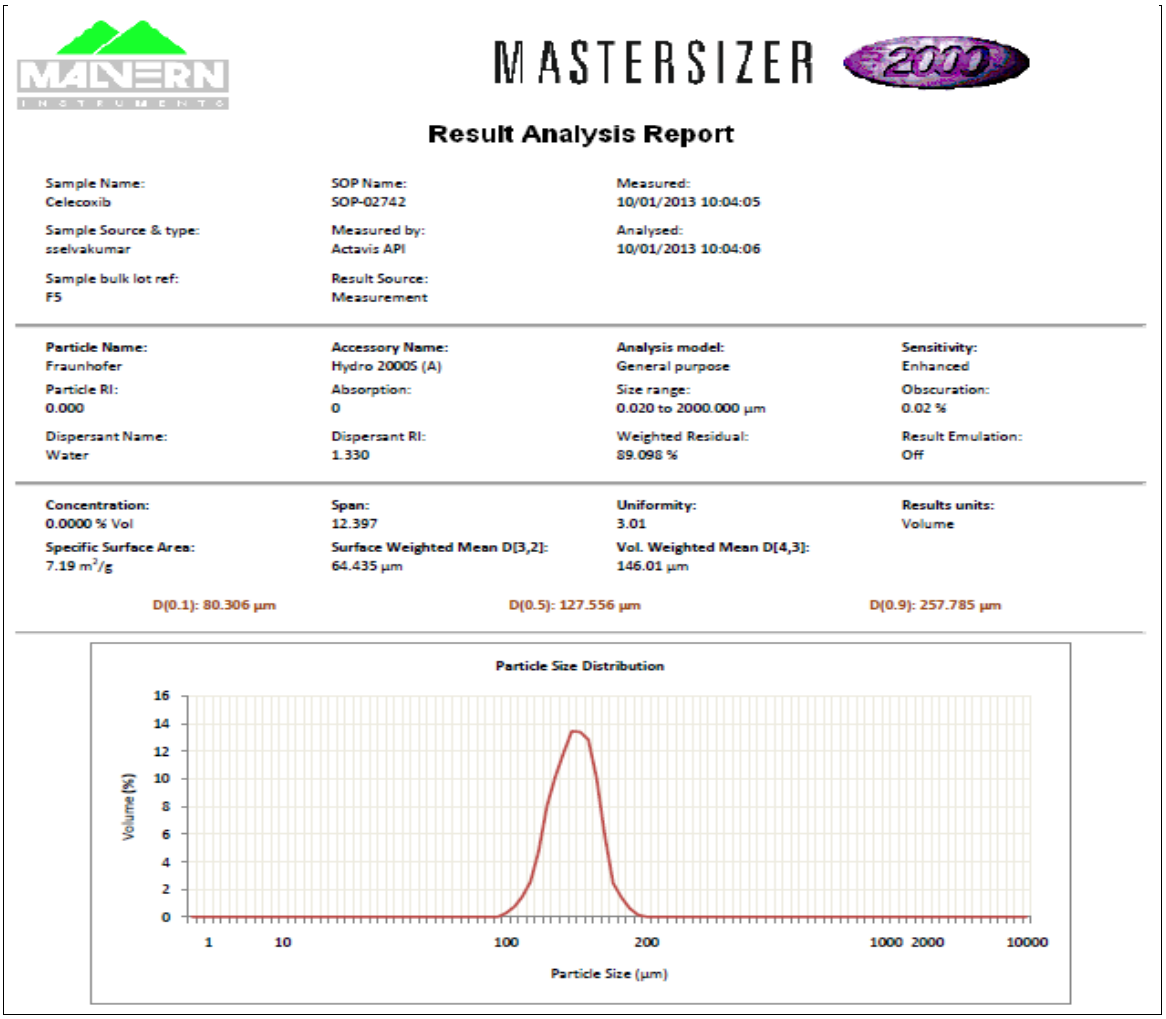

Figure 8.19 Particle size distribution of microparticulates

8.8.3 Scanning Electron Microscopy (SEM)

Surface morphology and shape characteristics of microparticulates for formulation F5 was evaluated by means of scanning electron microscopy. The SEM photographs of the microspheres revealed that the microparticulates were spherical with rough, hollow surface and slightly aggregated. The SEM photographs were provided in Figure 8.20.

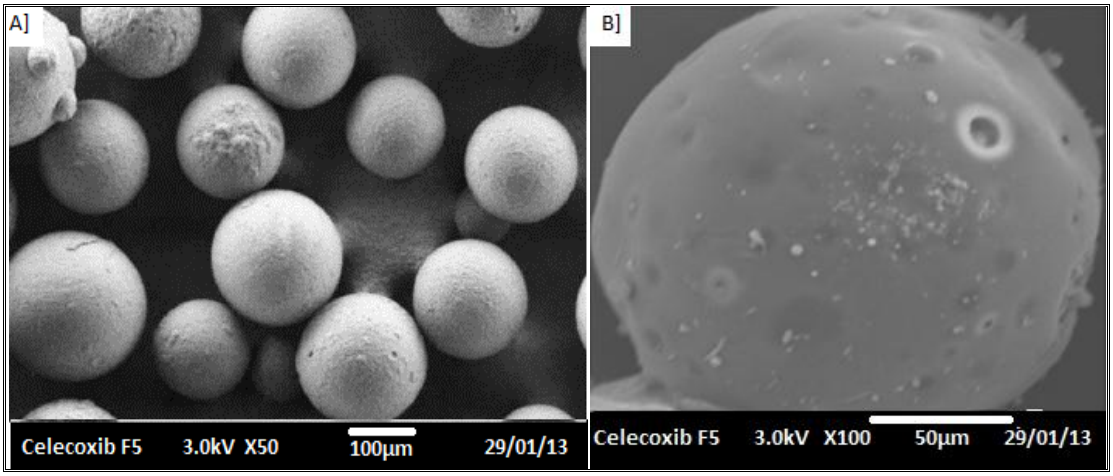

Figure 8.20 Scanning Electron Microscopy of microparticulates

8.8.4 Loss on Drying:

Loss on drying of microparticulates was determined at 105℃ for 3 hours. The loss on drying of all the formulated microparticulates were not more than 1 % w/w. From the results obtained in Loss on drying reveals that the microparticulates were dried efficiently at room temperature during formulation. The obtained results were represented in Table 8.17 and Figure 8.21.

Table 8.17 Loss on drying of microparticulates

Formulation No.	F1	F2	F3	F4	F5	F6	F7	F8	F9
Loss on Drying* (% w/w)	0.878 ± 0.003 %	0.912 ± 0.009 %	0.879 ± 0.002 %	0.859 ± 0.003 %	0.874 ± 0.001 %	0.880 ± 0.001 %	0.923 ± 0.001 %	0.841 ± 0.002 %	0.850 ± 0.004 %

* The values were expressed as Mean ± S.D., n = 3.

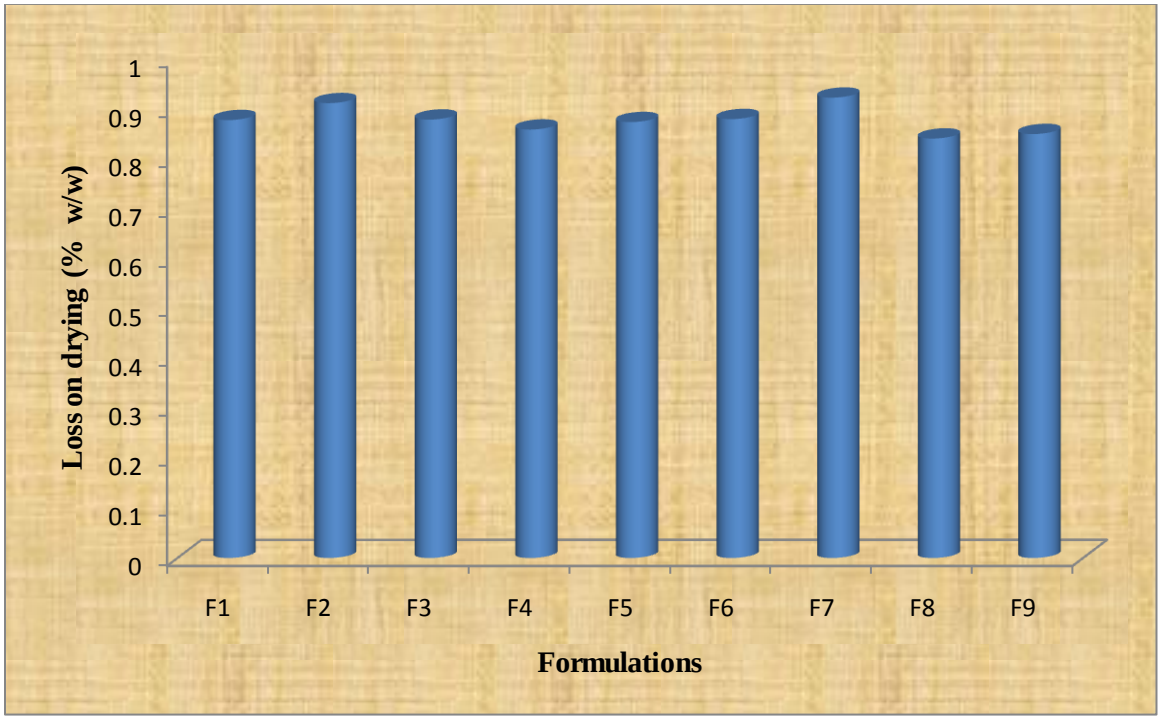

Figure 8.21 Loss on drying of microparticulates

8.8.5 Buoyancy Test and Entrapment efficiency:

The buoyancy percentage of non effervescent floating microparticulates was found to be in the range of 56.30 to 62.56 % Formulation F5 shows higher buoyancy percentage of 62.56%. The entrapment efficiency of non effervescent floating microparticulates was found to be in the range of 68.92 to 88.12 % Formulation F5 shows higher entrapment efficiency of 88.12%. The buoyancy percentage and entrapment efficiency of microparticulates were increased in formulations containing higher ratio of ethyl cellulose. The Buoyancy test and Entrapment efficiency of microparticulates were represented in Table 8.18 and Figure 8.22.

Table 8.18 Buoyancy test and Entrapment efficiency of microparticulates

Formulation No.	Buoyancy Test* (%)	Entrapment Efficiency* (%)
F1	57.87 ± 1.85	70.10 ± 1.52
F2	59.10 ± 1.37	80.96 ± 1.65
F3	60.31 ± 0.85	68.92 ± 2.30
F4	56.30 ± 1.69	74.80 ± 1.06
F5	62.56 ± 1.43	88.12 ± 1.84
F6	58.50 ± 1.23	69.68 ± 0.92
F7	56.81 ± 3.16	71.27 ± 1.63
F8	57.64 ± 0.77	77.51 ± 1.18
F9	56.73 ± 1.35	76.05 ± 0.74

* The values were expressed as Mean ± S.D., n = 3.

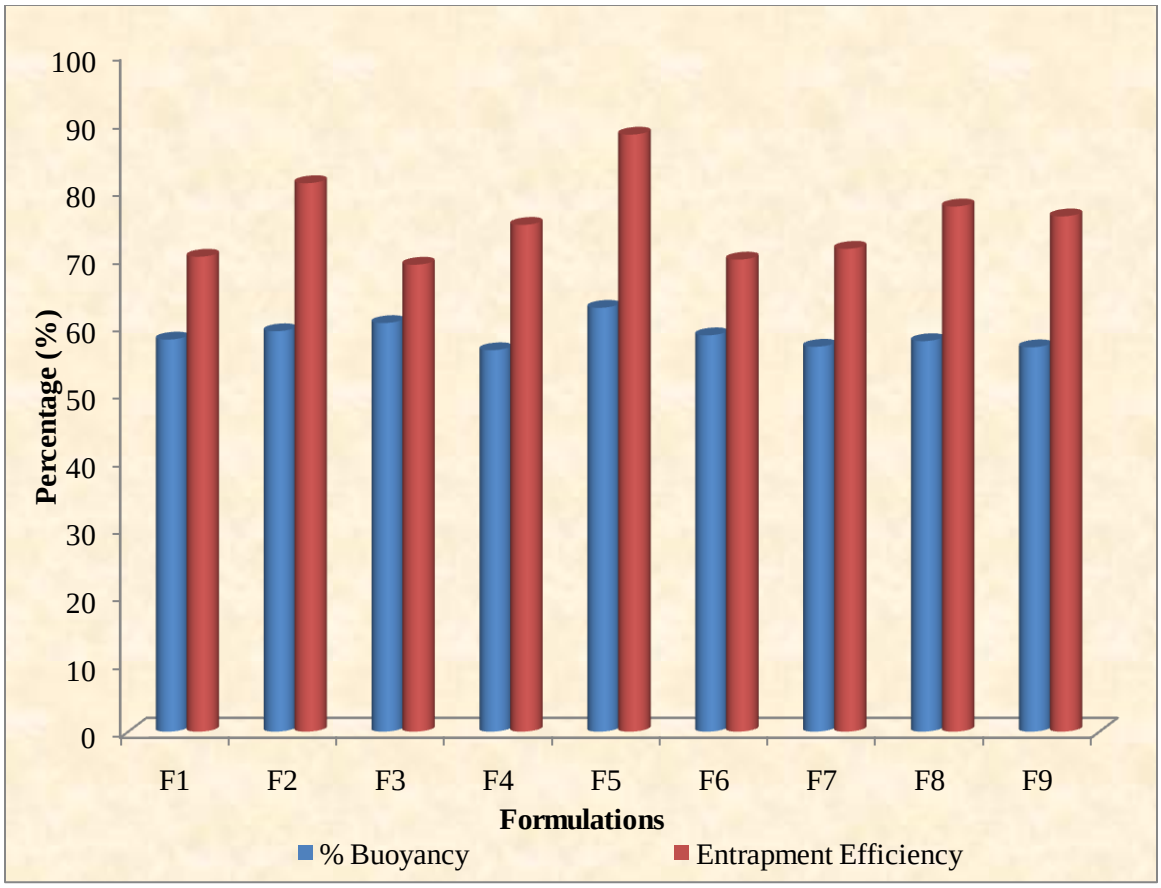

Figure 8.22 Buoyancy test and Entrapment efficiency of microparticulates

8.8.6 *In-vitro* Drug release studies:

The percentage drug release of non effervescent floating microparticulates were in the range of 64.23 to 83.52 %. Highest percentage drug release was found in F5 (83.52%), followed by F2 (76.09%), F8 (74.28%) and F9 (73.17%). From the results, it is evident that the formulations with increased ratio of ethyl cellulose shows increased percentage drug release.

The results of *in-vitro* drug release studies were represented in Table 8.19, and the respective plot for *in-vitro* drug release of Formulations F1 to F9 were represented in Figure 8.23 to 8.31. Graphical representation of *in-vitro* drug release studies were represented in Figure 8.32.

Table 8.19 *In-vitro* drug released profile of microparticulates for formulations F1 to F9

Time in Hours	Formulations *								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1 Hour	11.49	14.01	10.39	12.70	16.72	12.00	12.20	13.91	14.11
2 Hours	18.23	19.53	17.52	18.93	21.44	15.71	18.12	19.33	19.43
3 Hours	26.76	30.88	25.06	27.67	30.38	23.45	27.57	31.99	32.29
4 Hours	33.09	37.61	31.49	34.20	42.13	31.08	33.19	38.62	40.83
5 Hours	43.44	47.26	41.23	45.25	52.08	42.74	42.74	50.07	51.48
6 Hours	47.36	54.69	46.45	49.47	57.60	46.45	49.27	57.00	55.09
7 Hours	51.78	58.81	50.27	53.79	63.83	50.47	52.68	60.32	58.21
8 Hours	54.99	65.44	52.38	57.40	71.87	54.69	57.00	66.24	63.53
9 Hours	58.01	68.65	54.79	59.91	75.48	58.71	59.41	68.45	65.64
10 Hours	61.92	70.96	60.01	63.33	77.69	60.11	62.83	70.46	67.85
11 Hours	63.83	74.18	61.82	66.64	80.41	62.43	65.64	73.07	70.76
12 Hours	65.74	76.09	64.23	69.96	83.52	65.54	68.45	74.28	73.17

* The values were expressed as Mean ± S.D., n = 3.

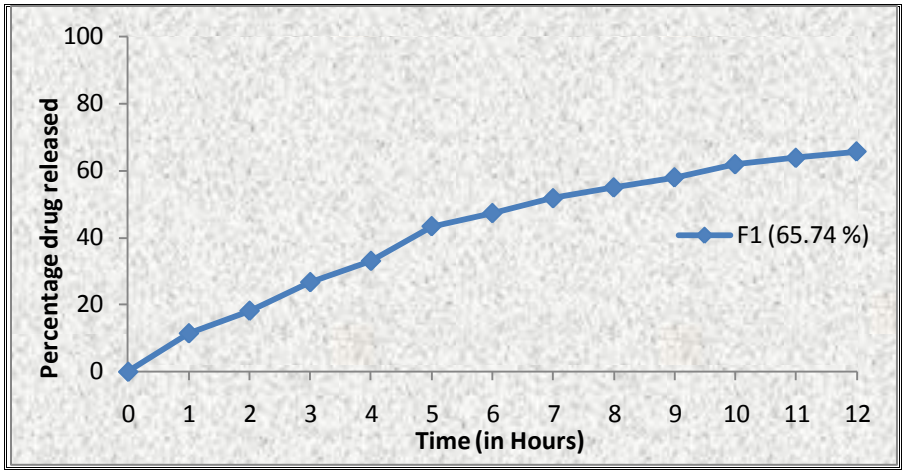

Figure 8.23 Plot of *in-vitro* drug released for Formulation F1

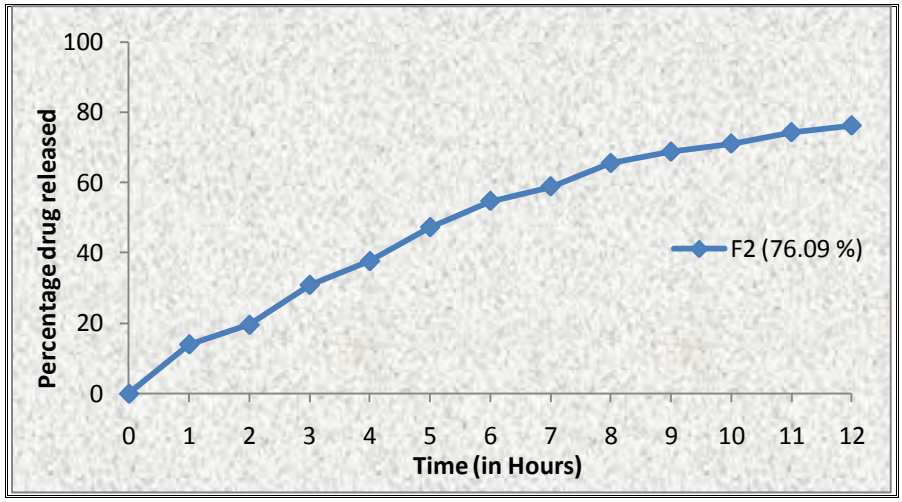

Figure 8.24 Plot of *in-vitro* drug released for Formulation F2

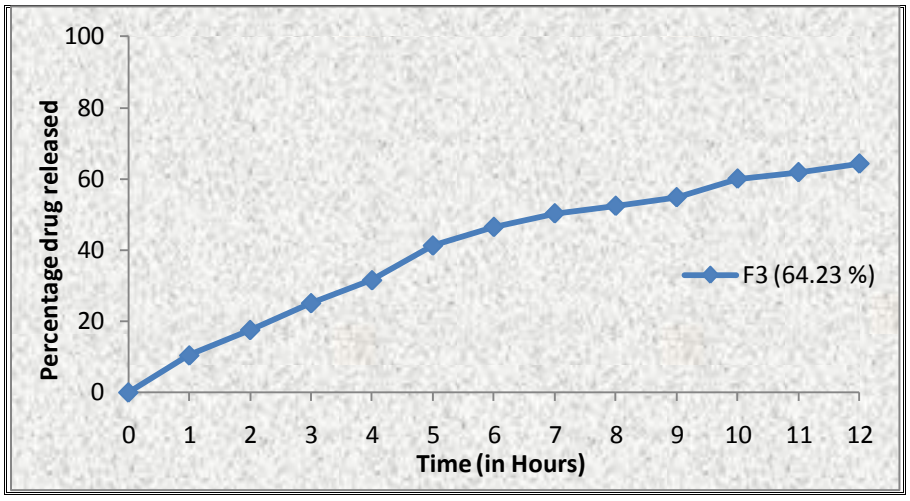

Figure 8.25 Plot of *in-vitro* drug released for Formulation F3

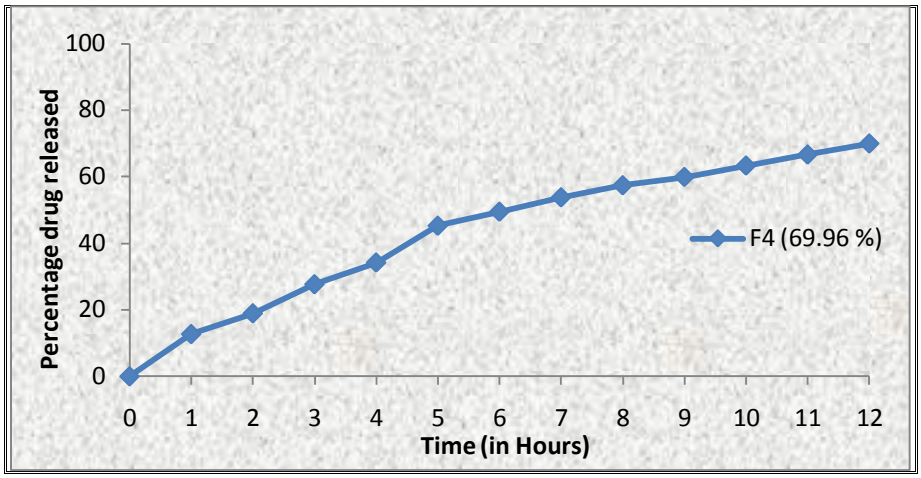

Figure 8.26 Plot of *in-vitro* drug released for Formulation F4

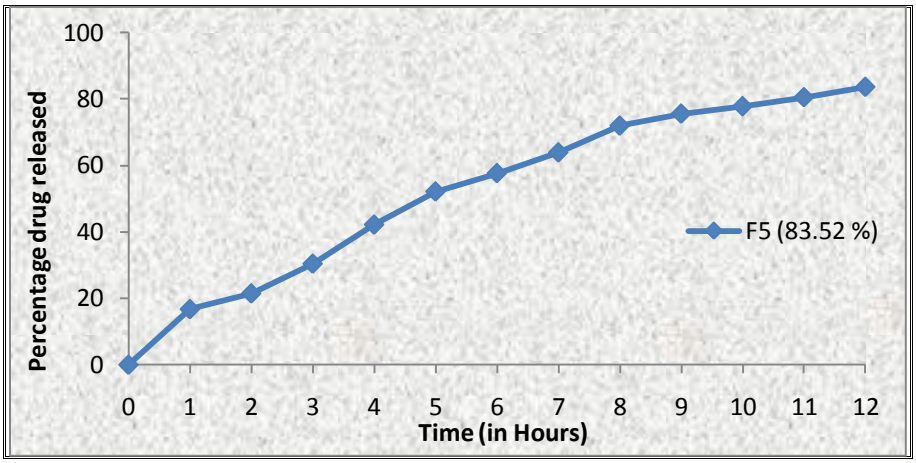

Figure 8.27 Plot of *in-vitro* drug released for Formulation F5

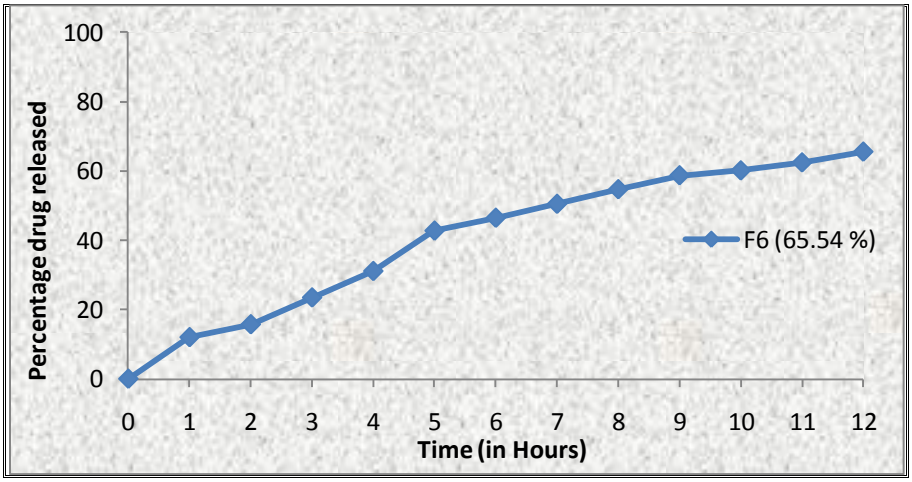

Figure 8.28 Plot of *in-vitro* drug released for Formulation F6

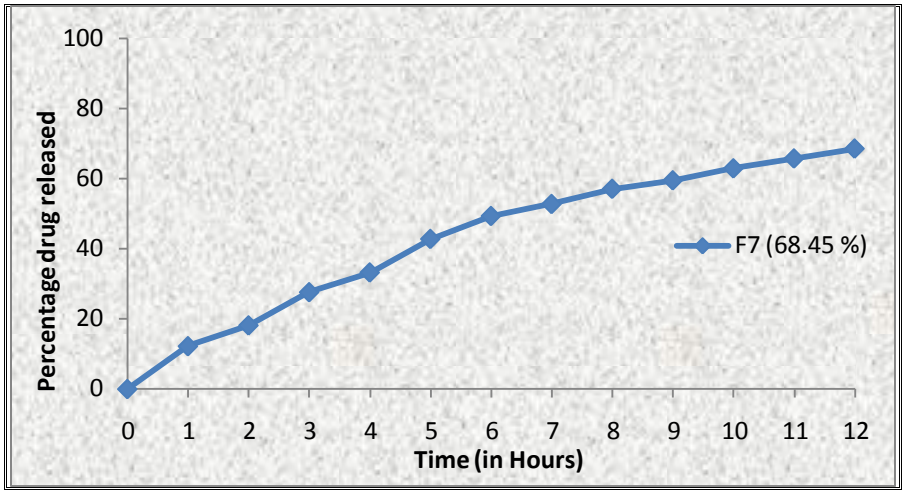

Figure 8.29 Plot of *in-vitro* drug released for Formulation F7

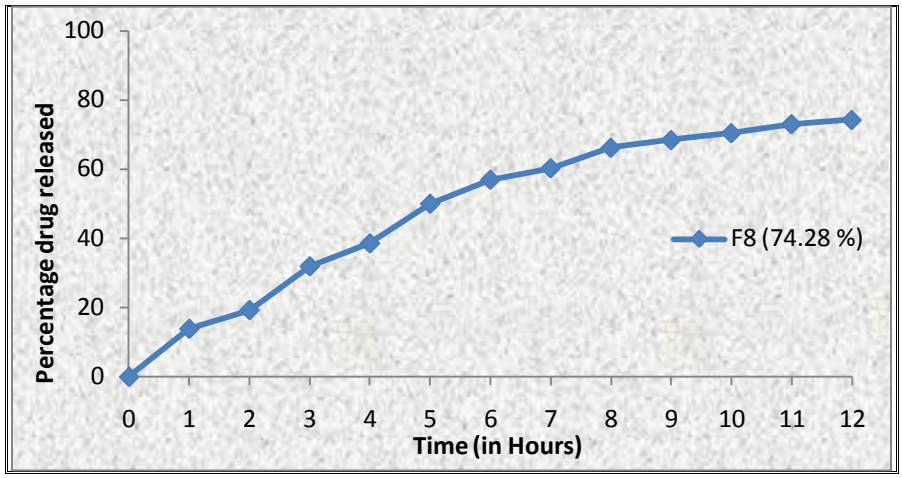

Figure 8.30 Plot of *in-vitro* drug released for Formulation F8

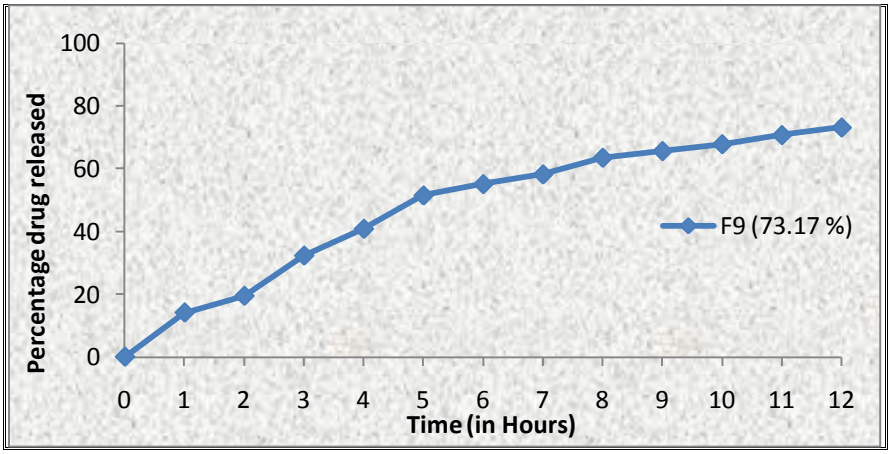

Figure 8.31 Plot of *in-vitro* drug released for Formulation F9

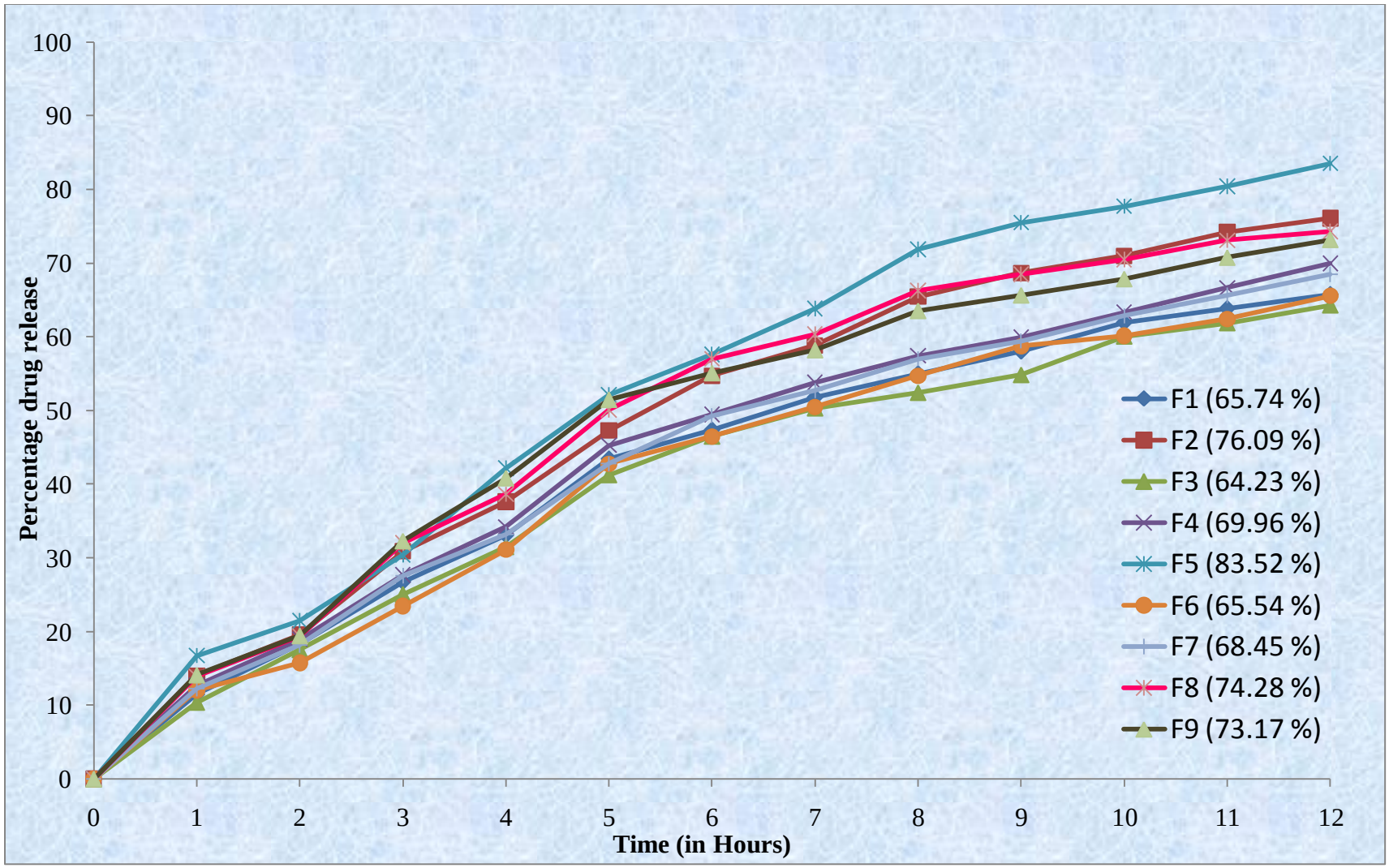

Figure 8.32 Plot of comprehensive *in-vitro* drug released profile of microparticulates for formulations F1 to F9

8.8.7 Kinetics of *in-vitro* drug release:

The kinetics of *in-vitro* drug release studies were determined by applying the drug release data to various kinetic models such as zero order, first order, Higuchi and Korsmeyer - Peppas. From the data and graphical representations, The interpretation release profile of Celecoxib non effervescent floating microparticulates were based on the regression coefficient values. Formulation F5 showed best fit model as first order kinetics. The results obtained were represented in Table 8.20 and the plot for kinetics of *in-vitro* drug released were represented in Figures 8.33 to 8.41.

Table 8.20 Kinetics of *in-vitro* drug release of microparticulates

Formulation No.	Zero Order	First Order	Higuchi	Peppas		Best Fit Model
	R^2	R^2	R^2	R^2	n	
F1	0.9326	0.9917	0.9894	0.9949	0.6403	Peppas
F2	0.9428	0.9975	0.9859	0.9928	0.6569	First Order
F3	0.9372	0.9909	0.9881	0.9955	0.6519	Peppas
F4	0.9346	0.9939	0.9887	0.9938	0.6348	First Order
F5	0.9473	0.9969	0.9838	0.9897	0.6519	First Order
F6	0.9423	0.9921	0.9833	0.9876	0.6557	First Order
F7	0.9375	0.9936	0.9877	0.9933	0.6428	First Order
F8	0.9263	0.9934	0.9862	0.9896	0.6531	First Order
F9	0.9126	0.9905	0.9895	0.9889	0.6306	First Order

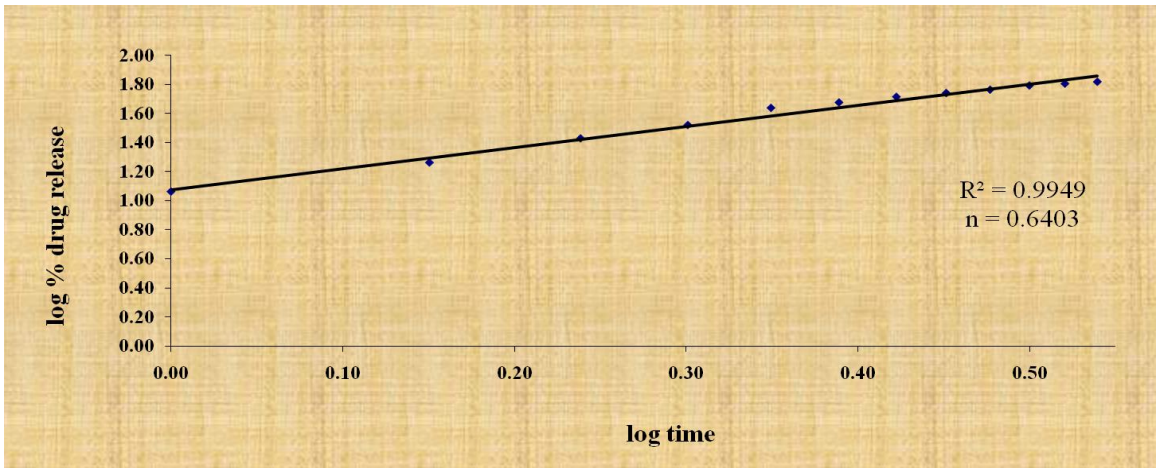

Figure 8.33 Best fit model (Peppas) for Formulation F1

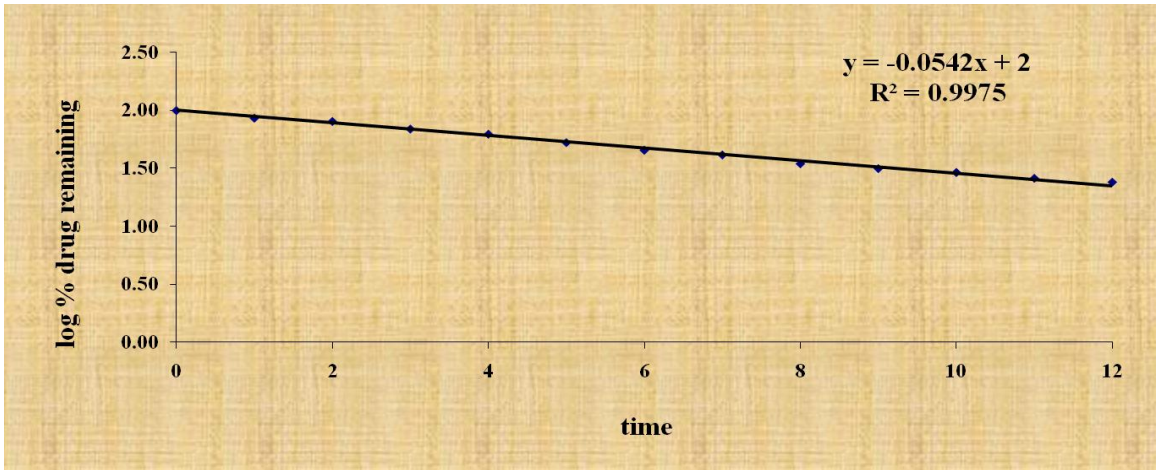

Figure 8.34 Best fit model (First order) for Formulation F2

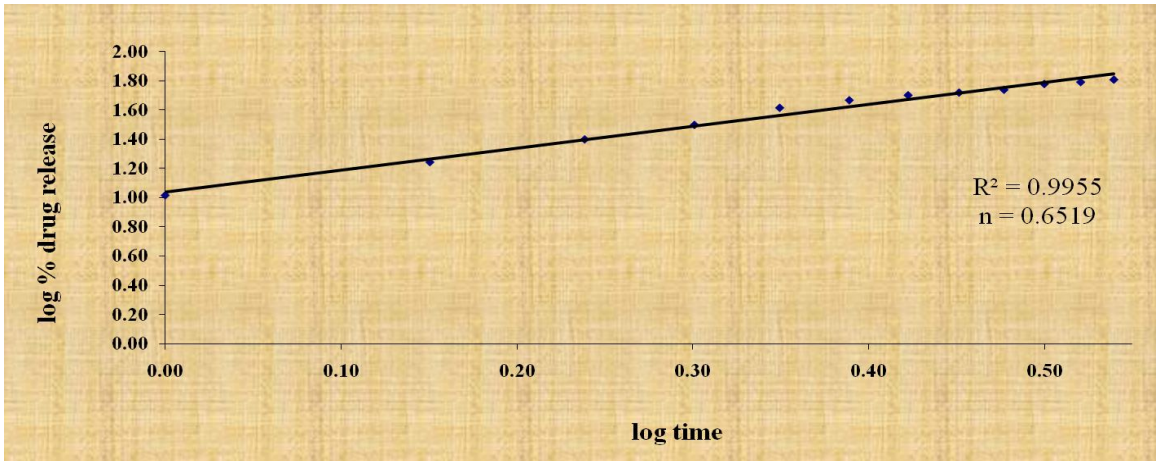

Figure 8.35 Best fit model (Peppas) for Formulation F3

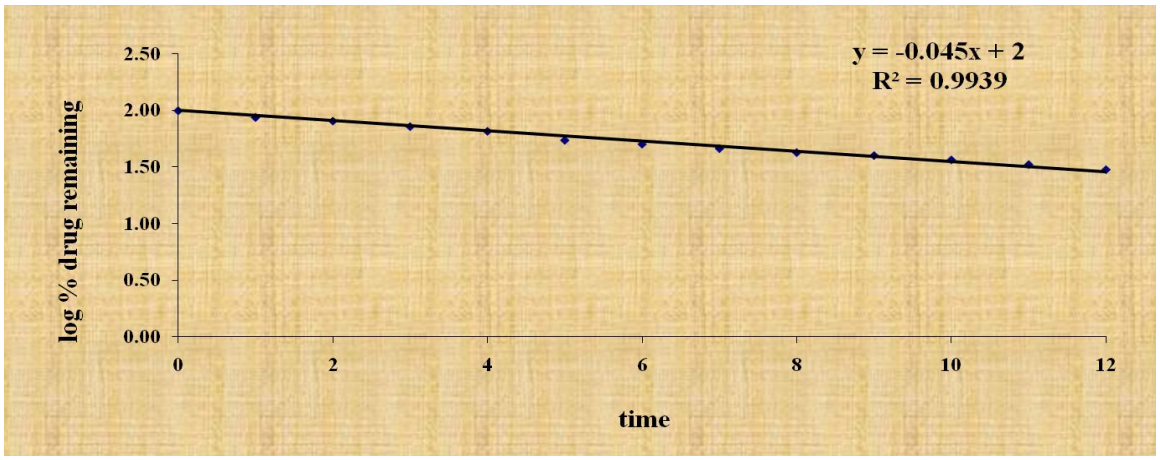

Figure 8.36 Best fit model (First order) for Formulation F4

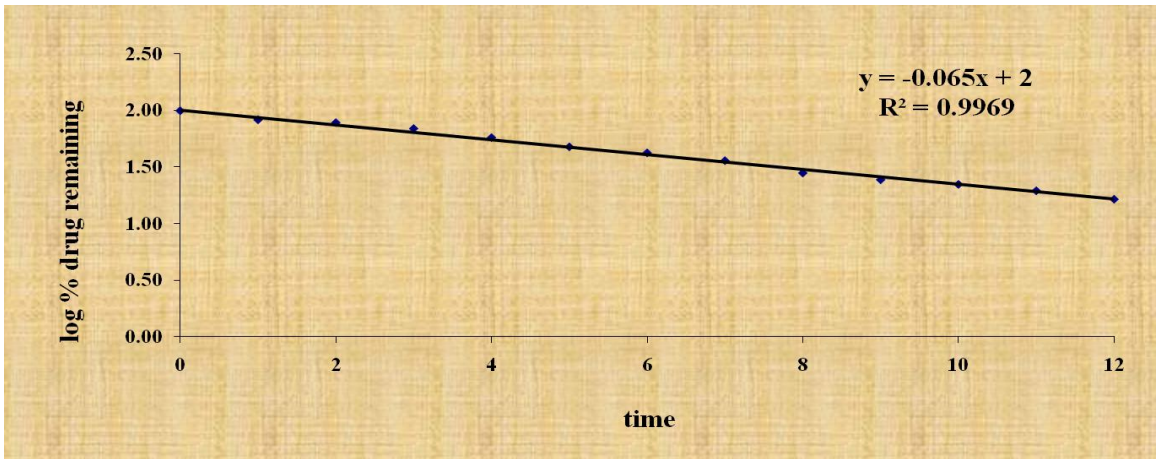

Figure 8.37 Best fit model (First order) for Formulation F5

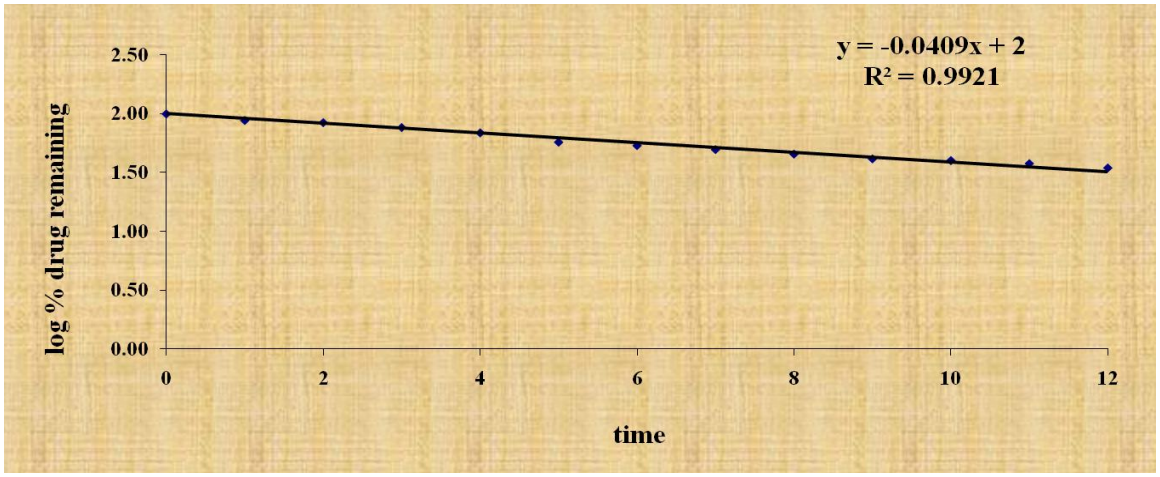

Figure 8.38 Best fit model (First order) for Formulation F6

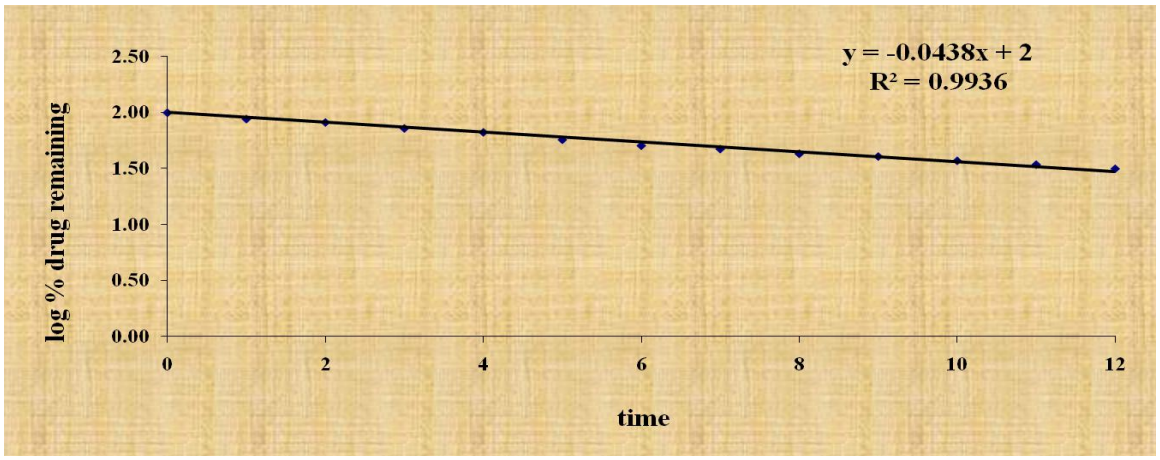

Figure 8.39 Best fit model (First order) for Formulation F7

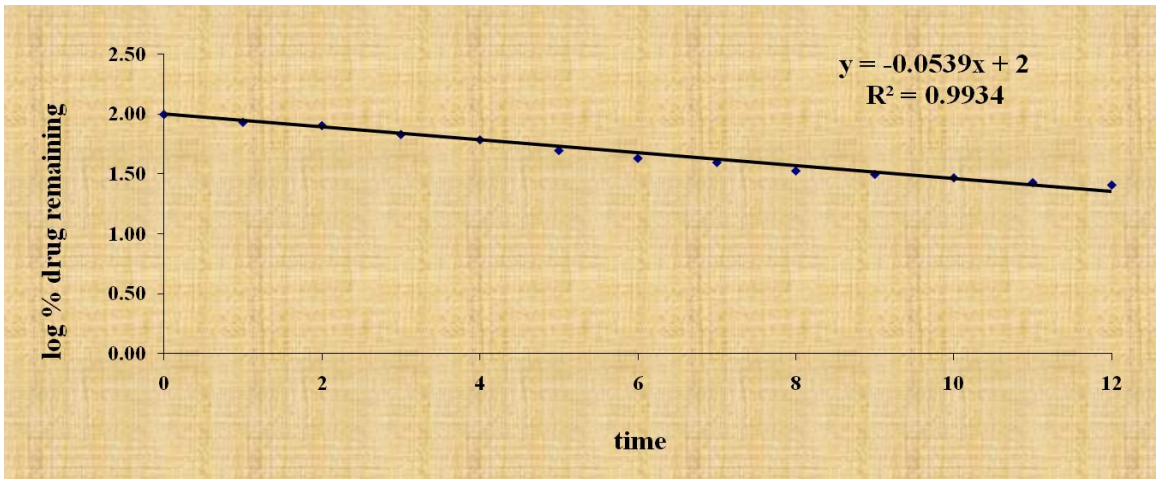

Figure 8.40 Best fit model (First order) for Formulation F8

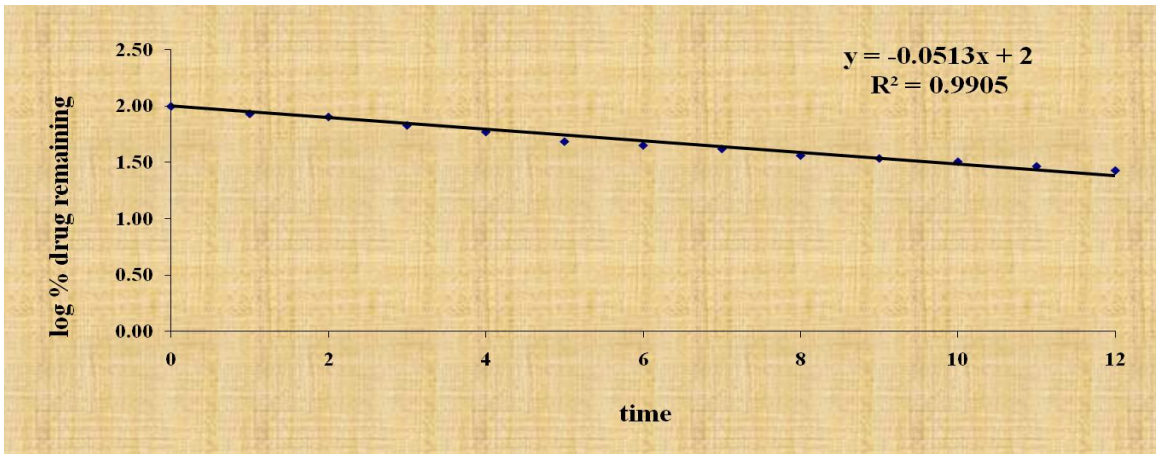

Figure 8.41 Best fit model (First order) for Formulation F9

8.8.8 *Ex-vivo* Permeation Studies:

The *ex-vivo* permeation study was performed using membrane obtained from goat stomach. The best formulation was selected based on the *in-vitro* drug release, Buoyancy percentage and entrapment efficiency. Formulation F5 results showed higher results of *in-vitro* drug release, Buoyancy percentage and entrapment efficiency, when compared with other formulations, so F5 was selected as best formulation.

The kinetics of *ex-vivo* permeation study was represented in Table 8.22 and the plot for kinetics of *ex-vivo* permeation study was represented in Figure 8.43.

Table 8.21 *Ex-vivo* Permeation Studies for formulation F5

Time (in Hours)	***Ex-vivo* Permeation Studies* (F5) (% Drug Released)**
1 Hour	5.72 ± 1.67
2 Hours	10.60 ± 0.75
3 Hours	15.39 ± 1.23
4 Hours	20.97 ± 0.85
5 Hours	25.75 ± 1.10
6 Hours	30.84 ± 0.54
7 Hours	36.42 ± 0.28
8 Hours	41.10 ± 1.06
9 Hours	44.99 ± 1.02
10 Hours	51.66 ± 1.02
11 Hours	56.45 ± 0.67
12 Hours	62.02 ± 1.34

* The values were expressed as Mean ± S.D., n = 3.

The percentage drug released at *ex-vivo* permeation study for formulation F5 at 12 hours was found to be 62.02 %. The percentage drug released at *ex-vivo* permeation study (62.02 %) was found lesser than the percentage drug released at *in-vitro* drug release study (83.52 %) for formulation F5. The results of *ex-vivo* permeation studies was represented in Table 8.21, and the plot for *ex-vivo* permeation studies were shown in Figure 8.42.

The kinetics of *ex-vivo* permeation study was determined by applying the drug released data to various kinetic models such as zero order, first order, Higuchi and Korsmeyer - Peppas. The best fit model for kinetics of *ex-vivo* permeation study was found to be Zero order kinetics.

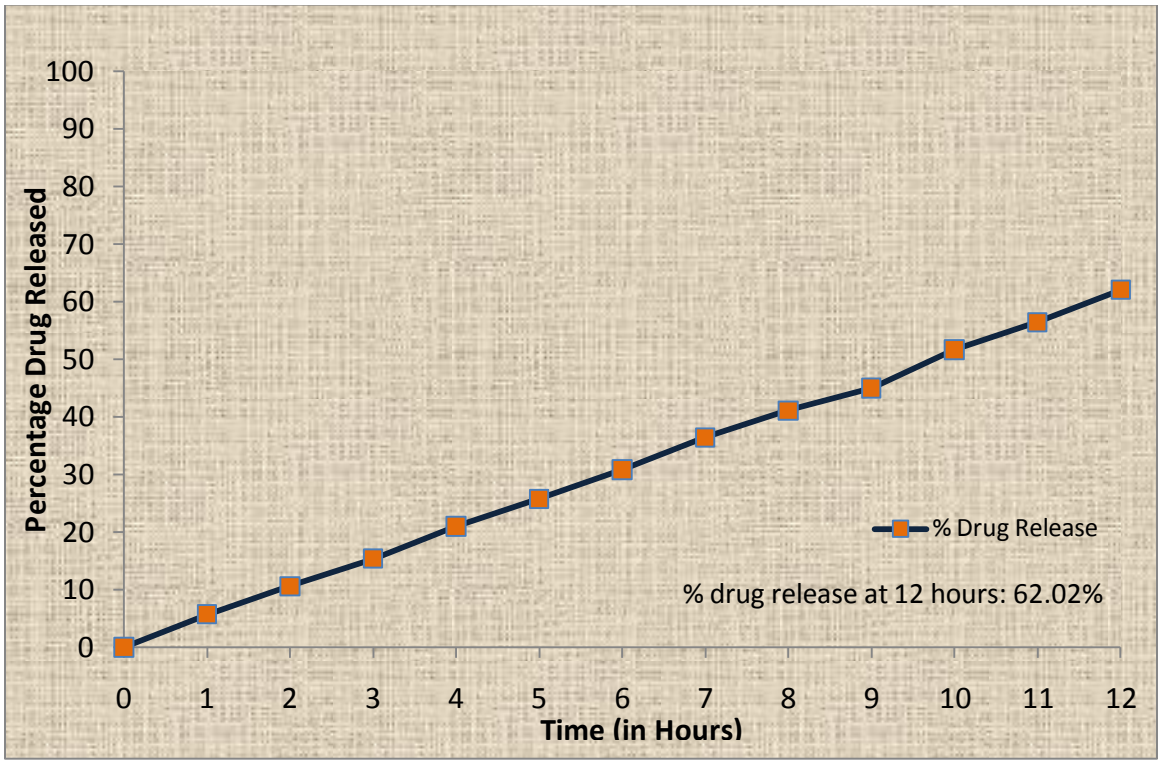

Figure 8.42 *Ex-vivo* Permeation Studies of Formulation F5

Table 8.22 Kinetics of *ex-vivo* Permeation Studies for formulation F5

Formulation No.	Zero Order	First Order	Higuchi	Peppas		Best Fit Model
	R^2	R^2	R^2	R^2	n	
F5	0.9936	0.9879	0.9501	0.9926	0.7735	Zero Order

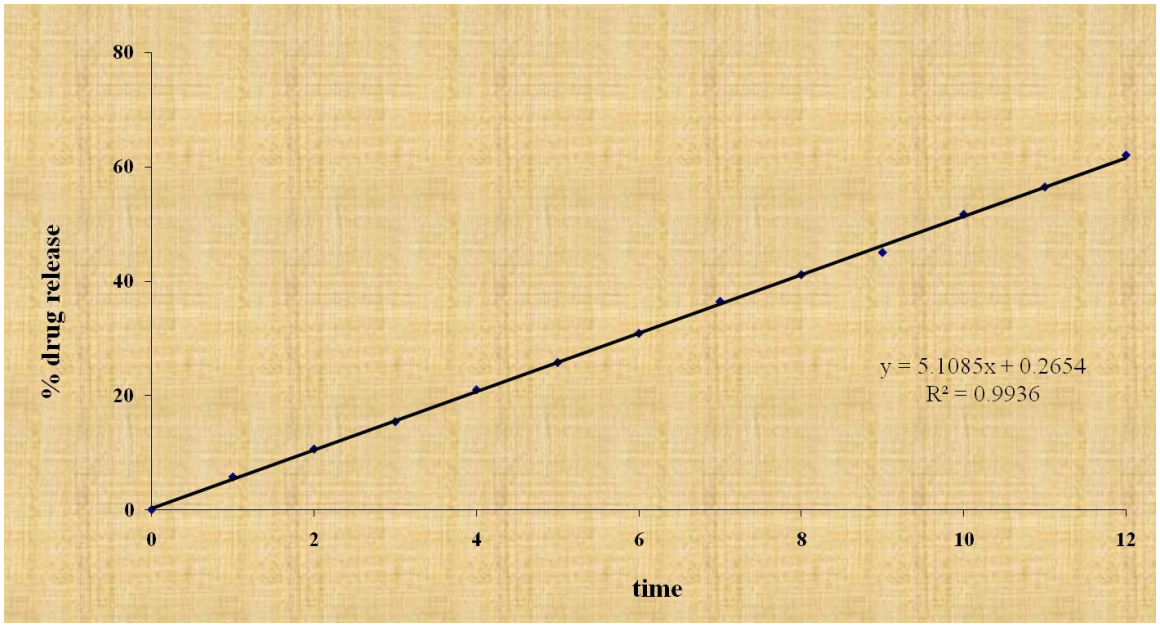

Figure 8.43 Best fit model (Zero order) for *ex-vivo* Permeation Studies of Formulation F5

8.8.9 Stability Studies:

The best formulation F5 was further subjected to stability studies at room temperature. After specified period of stability, the samples were analysed for *in-vitro* drug release and Buoyancy studies.

A] *In-vitro* drug release studies:

Stability study results of *in-vitro* drug release study was found to be 83.08 % at third month stability testing. When compared with initial results of *in-vitro* drug release study (83.52%), the formulation F5 shows no significant change at room temperature.

The stability study results of *in-vitro* drug release study were represented in Table 8.23, and the respective plot for *in-vitro* drug release were shown in Figure 8.44.

Table 8.23 Stability Studies – *In-vitro* Drug Release for formulation F5

Time (in Hours)	DURATION*			
	Initial	1 month	2 month	3 month
1 Hour	16.72 ± 0.80	13.13 ± 0.99	13.05 ± 0.30	12.93 ± 0.13
2 Hours	21.44 ± 0.92	20.83 ± 0.83	20.66 ± 0.72	20.43 ± 0.43
3 Hours	30.38 ± 1.14	30.22 ± 0.68	30.17 ± 0.51	30.02 ± 0.59
4 Hours	42.13 ± 1.25	41.61 ± 1.00	41.48 ± 0.83	41.21 ± 1.10
5 Hours	52.08 ± 1.36	51.40 ± 1.10	51.29 ± 0.88	51.10 ± 1.14
6 Hours	57.60 ± 1.49	56.90 ± 1.27	56.79 ± 1.15	56.70 ± 1.31
7 Hours	63.83 ± 2.22	62.89 ± 2.10	62.80 ± 1.91	62.59 ± 1.75
8 Hours	71.87 ± 2.28	71.49 ± 1.32	71.01 ± 2.06	70.68 ± 1.41
9 Hours	75.48 ± 1.81	74.78 ± 1.47	74.71 ± 1.34	74.58 ± 1.10
10 Hours	77.69 ± 1.52	77.18 ± 1.01	77.11 ± 0.87	76.98 ± 0.52
11 Hours	80.41 ± 1.22	79.38 ± 1.17	79.21 ± 1.03	78.88 ± 0.92
12 Hours	83.52 ± 0.63	83.48 ± 0.35	83.32 ± 0.35	83.08 ± 0.90

* The values were expressed as Mean ± S.D., n = 3.

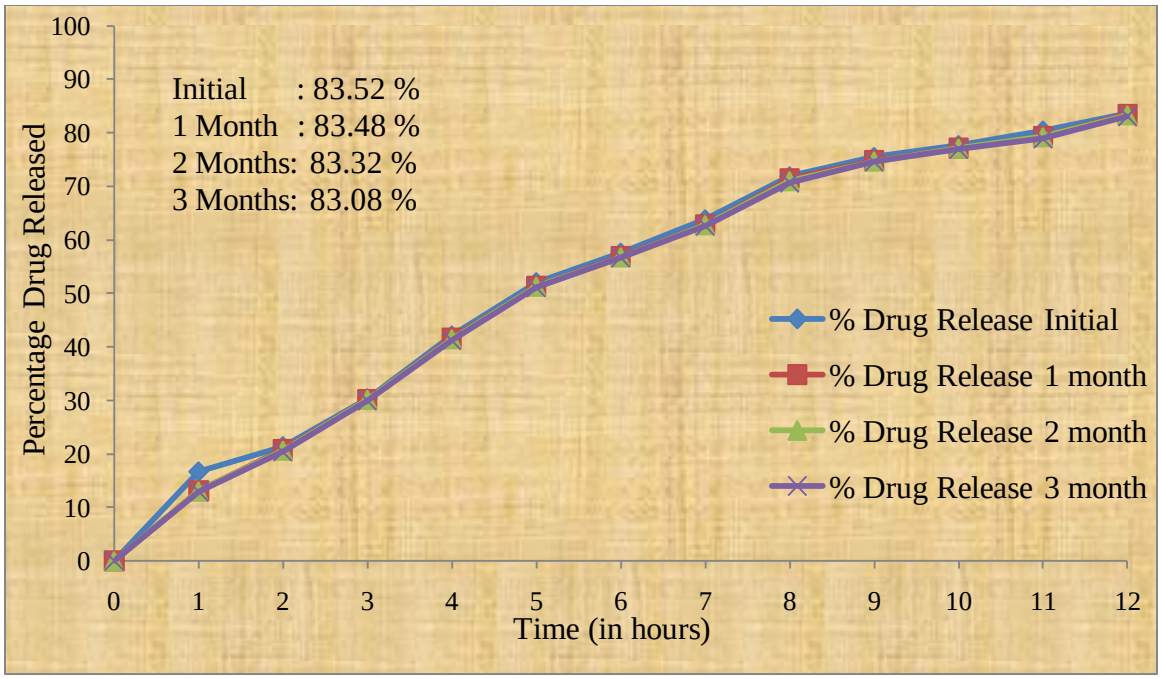

Figure 8.44 Stability Studies – *In-vitro* Drug Release

B] Buoyancy Test:

The stability study results of percentage buoyancy were represented in Table 8.24, and the respective plot for percentage buoyancy were shown in Figure 8.45.

Table 8.24 Stability Studies – Buoyancy Test for formulation F5

Stability Period	Initial	1 month	2 month	3 month
Buoyancy* (%)	62.56 ± 1.43	62.50 ± 0.62	62.33 ± 0.87	62.19 ± 0.62

* The values are expressed as Mean ± S.D., n = 3.

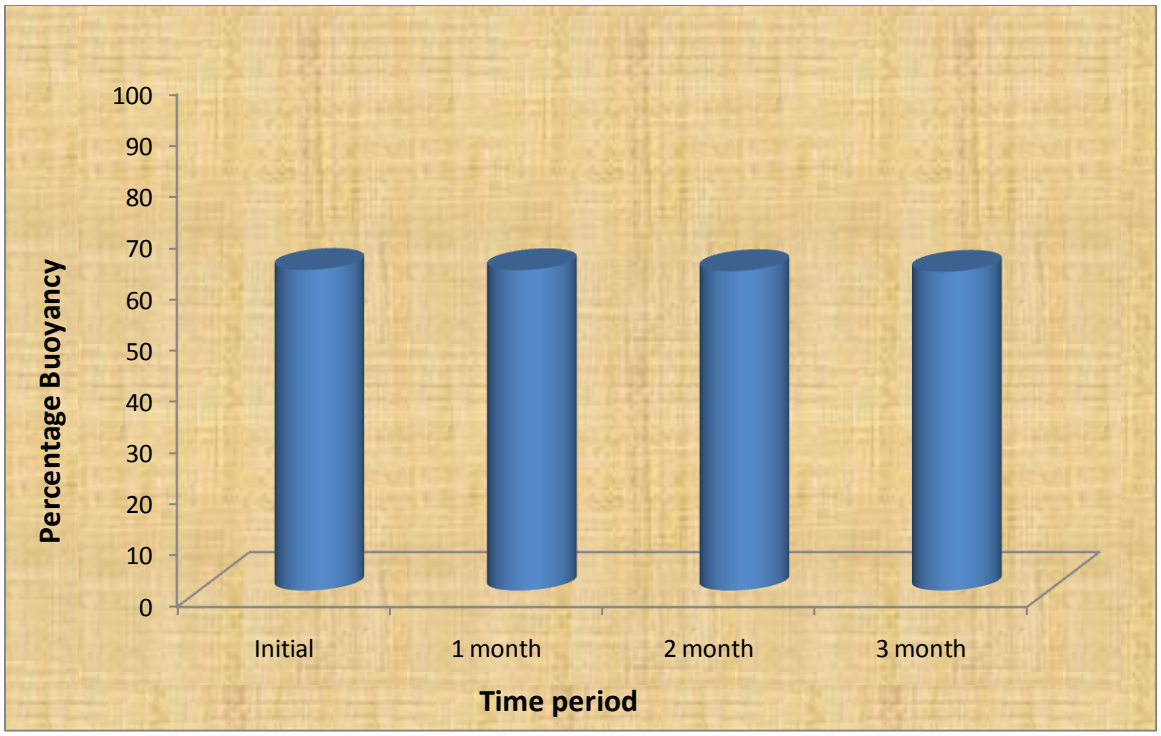

Figure 8.45 Stability Studies – Buoyancy Test

Stability study results of percentage buoyancy was found to be 62.19 % at third month stability testing. When compared with initial results of percentage buoyancy (62.56 %), the formulation F5 shows no significant change at room temperature.

SUMMARY AND CONCLUSION

9. SUMMARY AND CONCLUSION

Celecoxib is the first selective COX-2 inhibitor which is widely used in the treatment of Osteoarthritis, Rheumatoid Arthritis and management of pain. USFDA has approved its use Osteoarthritis, Rheumatoid Arthritis with a dose of 100 to 200 mg once / twice daily.

This research work mainly focus on the therapeutic effect of the drug to increased bioavailability. According to the BCS classification, Celecoxib is class II compound, which is low solubility and high permeability. Oral bioavailability is determined by rate of drug release in GI tract.

Development of new drug molecule was expensive and time consuming. Improving safety efficacy ratio of "old" drugs has been attempted using different methods such as individualizing drug therapy, dose titration and therapeutic drug monitoring. Delivering drug at controlled rate, slow delivery and targeted delivery are other very attractive methods.

Many attempts have been made in recent years to provide a dosage form with longer gastro-retention time and therefore a more efficient absorption. Floating drug delivery system are well proved and documented to be therapeutically superior to conventional dosage system in number of studies. Hence the aim was to develop non effervescent floating microparticulates of Celecoxib with the view to prolonged the residence time within the GI tract with a controlled release of the drug.

The identification of drug was carried out by FTIR spectroscopy and melting point. The physicochemical parameters such as color, odor, taste, solubility study and loss on drying were performed. The analytical profile of drug was evaluated for determination of absorption maximum, development of standard curve and percentage purity of drug.

Compatibility of drug and polymer mixtures were done by performing FTIR and DSC study. It was concluded that there were **no interaction** between drug and polymers.

Nine different formulations were prepared with different concentration and combination of polymers (Ethyl cellulose and HPMC K15M). Celecoxib microparticulates were prepared by **solvent diffusion and evaporation method**. All the formulations were evaluated for Appearance, Percentage yield, Micromeritic properties, Particle size, Loss on drying, Buoyancy test, Entrapment efficiency, *In-vitro* drug release and Kinetics of *in-vitro* drug release.

On comparing the major criteria in evaluation such as *in-vitro* drug release, Buoyancy percentage and entrapment efficiency, the Formulation F5 showed results of *in-vitro* drug released (83.52%), Buoyancy percentage (62.56%) and entrapment efficiency (88.12%), were compared with all formulations F1 to F9. The buoyancy percentage, entrapment efficiency and *in-vitro* drug release of microparticulates were increased in formulations with higher ratio of ethyl cellulose. The formulation F5 was selected as the best formulation among the nine formulations (F1 to F9) were prepared.

The kinetics of *in-vitro* drug release studies were determined by applying the drug released data to various kinetic models such as zero order, first order, Higuchi and Korsmeyer - Peppas. The formulation F5 was best fitted with first order kinetics.

Surface morphology by SEM analysis, *ex-vivo* permeation study and stability studies were carried out for the best formulation F5. The *ex-vivo* permeation study was performed using membrane obtained from goat stomach.

All the stability studies for the formulation F5 at room temperature was showed **no significant change** in the percentage drug release studies and percentage buoyancy.

The **formulation F5** was concluded best formulation among the formulations were prepared.

FUTURE PROSPECTUS

10. FUTURE PROSPECTUS

In the field of gastric retention, there are many obstacles that need to be overcome in order to be able to claim true gastric retention. Considering the advantages for improved delivery of drugs, further clinical studies are needed to access the utility of this system for patients suffering from Rheumatoid arthritis and Osteoarthritis.

This dosage forms holds promise for further systems. *In-vitro – in-vivo* correlation (IVIVC) will serve as a means of modeling the human organism and of gaining a better understanding of drug absorption and its dependence on *in-vitro* release process.

Convincing results of clinical studies have yet to be obtained for a gastroretentive system that displays the necessary performance behavior and which is retained in the fasted stomach of humans for a sensible period of time after dosing. Furthermore, the system will need to retain its integrity for an extended period of time in the harsh conditions present in the human stomach.

Once the technology is fully accepted, these systems will probably increase with new pipeline drugs that need enhancement to their bioavailability.

Finally, while the control of drug release profiles has been a major aim of pharmaceutical research and development in the past two decades, the control of GI transit profiles could be the focus of the next two decades and might result in the availability of new products with new therapeutics possibilities and substantial benefits for patients. Soon, the novel gastro-retentive products with release and absorption phases of approximately 24 hr will surely hit the market.

BIBLIOGRAPHY

11. BIBLIOGRAPHY

1. Ajit K. and Manish B. Development and evaluation of regioselective bilayer floating tablets of Atenolol and Lovastatin for biphasic release profile. Iranian Journal of Pharmaceutical Research, **2009**, 8 (1), 15-25.
2. Amitava G, Somnath B. and Simli S. Mechanism and Kinetics of drug release from polymers: An overview. Journal of Pharmacy Research, **2009**, 2 (2), 158-162.
3. Anand P, Moin M, Dushyant S. and Vishnu P. Development and *in-vivo* floating behavior of Verapamil hydrochloride intragastric floating tablets. AAPS Pharm Sci Tech, **2009**, 10 (1), 310-315.
4. Anilkumar J.S. and Harinath M.N. Gastroretentive drug delivery system: An Overview. Pharmaceutical reviews, **2008**, 6(1), 1-9.
5. Anonymous, The Indian Pharmacopoeia. Vol-1, 2, 3, The Controller of publication, New Delhi, **2007**, 1745-1750.
6. Anonymous, The Merck Index. An encyclopedia of chemicals, drugs and biologicals. 14th edn., New Jersy, Merck and Co. Inc, **1997**. 1510.
7. Anonymous. http://en.wikipedia.org/wiki/Differential_scanning_calorimetry
8. Anonymous. http://en.wikipedia.org/wiki/Fourier_transform_infrared_spectroscopy
9. Anonymous. http://www.drugbank.ca/drugs/DB00482
10. Anonymous. http://www.ethocel.com
11. Anonymous. United States Pharmacoepiea, First Supplement to USP 35–NF 30, **2012**, 5360, 5447–5448.
12. Aulton M.E. Eds. Pharmaceutics: The science of dosage form design. 2nd edn., Churchill Livingstone, New York, **2002**, 270-278.

13. Bandyopadhyay A.K. Novel drug delivery systems. 1st edn., Everest publishing house, Pune, **2008**, 161-175.
14. Bankar G.S. and Rhodes C.T. Eds. Modern Pharmaceutics. 3rd edn, Marcel Dekker, Inc. New York, **2009**, 501-578.
15. Baumgartner S, Kristel J, Vreer F, Vodopivec P. and Zorko B. Optimisation of floating matrix tablets and evaluation of their gastric residence time. International Journal of Pharmaceutics, **2000**, 195, 125-135.
16. Bindu Madhavi B., Zulkar Nain Kamal M., Kusum B. and David Banji. Formulation and Evaluation of Venlafaxine Hcl Microspheres, Hygeia Journal for Drugs and Medicines, **2011**, 64-70.
17. Brahmankar D.M. and Jaiswal S.B. Biopharmaceutics and Pharmacokinetics A Treatise. 1st edn., Vallabh Prakashan, New Delhi, **1995**, 50-57.
18. Chein YW. Novel Drug Delivery Systems, 2nd edn, CRC Press Bioadhesive Drug Delivery Systems, **1995**, 11-18.
19. Dalavi V.V. and Patil J.S. Gastroretentive drug delivery system of an antiretroviral agent. International Journal of Pharm Tech Research. **2009**, 1 (4), 1678-1684.
20. Dave B.S, Amin A.F. and Patel M.M. Gastroretentive drug delivery system of ranitidine hydrochloride: formulation and *in-vitro* evaluation. AAPS Pharm Sci Tech, **2004**, 5, 1-6.
21. Dhawale S.C. and Patil P.S. Floating drug delivery for controlled release of Acyclovir. Indian drugs, **2009**, 46(10), 44-48.
22. Fabián Teixeira Primo and Pedro E. Fröehlich. Celecoxib Identification Methods. Acta Farm. Bonaerense, **2005**, 24 (3), 421-5.

23. Garg R. and Gupta G.D. Progress in controlled gastroretantive delivery systems. Tropical journal of pharmaceutical research, **2008**, 7 (3), 1055-1066.

24. Harris M.S, Jaweria T, Hamid A.M. and Rabia I.Y. Evaluation of drug release kinetics from ibuprofen matrix tablets using HPMC. Pak J Pharm Sci, **2006**, 19(2), 119-124.

25. Hoffman A, Klausner E.A, Eran L, and Michael F. Expandable gastroretentive dosage forms. Journal of Controlled Release, **2003**, 90, 143–162.

26. Jaimini M, Rana A.C. and Tanwar Y.S. Formulation and Evaluation of Famotidine Floating Tablets. Current Drug Delivery, **2007**, 4, 51-55.

27. Jain N.K. Progress in controlled and novel drug delivery system. 1st edn., CBS Publisher and distributers, New Delhi, **2004**, 79-86.

28. Karade Preeti G, Shah Rohit R, Chougule DD and Bhise SB. Formulation and evaluation of Celecoxib Gel, Journal of Drug Delivery and Therapeutics; **2012**, 2(3): 132-135

29. Kedar Prasad Meena, Dangi J.S, Samal P.K. and Namdeo K.P. Recent Advances in Microspheres Manufacturing Technology, International Journal of Pharmacy and Technology, **2011**, 854-893.

30. Kim H.K. and Singh B.N. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. Journal of Controlled Release, **2000**, 63, 235–259.

31. Kishan V, Ramesh B, Rongala A.S. and Madhusudan R.Y. Development and evaluation of gastro retentive norfloxacin floating tablets. Acta Pharm, **2009**, 59, 211–221.

32. Kshirsagar R.V, Vikas J. and Wattamwar S. Effect of different viscocity grade HPMC polymers on gastroretantive drug delivery of Metformin HCL. International journal of applied pharmaceutics, **2009**, 1 (1), 44-50.
33. Lachman L, Lieberman H.A. and Kanig J.L. The theory and practice of industrial pharmacy. 3rd edn., Varghese Publishing House, Mumbai, **1991**, 67-71, 183-184.
34. Margret C.R, Debjit B.C. and Jayakar B. Formulation and evaluation of gastroretentive drug deliverysystem of gastroprokinetic drug itopride hydrochloride. International journal of pharmacy and pharmaceutical sciences, **2010**, 2 (1), 53-65.
35. Mayavanshi A.V. and Gajjar S.S. Floating drug delivery systems to increase gastric retention of drugs: A Review. Research Journal of Pharmacy and Technology, **2008**, 1(4), 345-48.
36. Mohammed Mostafa Ibrahim, Abd-Elgawad Helmy Abd-Elgawad, Osama Abd-Elazeem Soliman and Monica M. Jablonski. Nanoparticle-based topical ophthalmic formulations for sustained celecoxib release. Journal of Pharmaceutical Sciences. **2013**, Issue 3, 1036–1053.
37. Patel V.F. and Natavaral M. Patel, Intragastric floating drug delivery system of Cefuroxime Axetile: *In-vitro* evaluation. AAPS PharmaSciTech, Article1, **2006**, (E1-E7).
38. Patil J.M, Hirlekar R.S, Gide P.S. and Kadam V.J. Trends in floating drug delivery systems. Journal of Scientific and Industrial research, **2006**, 65, 11-21
39. Patil S.V, Kuchekar B.S, Janugade B.U. and Lade P.D. *In-vitro* Studies of Stavudine Sustained Release from Hydrophilic Matrices. Journal of Pharmacy Research, **2009**, 2(12), 1855-1856.

40. Prajapati S.T, Laxmanbhai D.P. and Chhaganbhai N.P. Floating matrix tablets of domperidone: formulation and optimization using simplex lattice design. Thai J. Pharm. Sci, **2009**, 33, 113-122.

41. Prakash R.C, Neelma A.K, Snehith V.S. and Ramesh C. Development of Gastro Retantive Drug Delivery Systems of cephalexin by using factorial design. ARS Pharmaceutica, **2009**, 50(1), 8-24.

42. Punitha S, Karthikeyan D, Devi P, Vedha Hari B.N. Enhancement of Solubility and Dissolution of Celecoxib by Solid Dispersion Technique. Journal of Pharmaceutical Science and Technology Vol. 1 (2), **2009**, 63-68.

43. Rajesh K, Usharani E, Nagaraju R, Haribabu R. and Siva P.R. Design and Evaluation of Sustained release Floating tablets for the treatment of Gastric Ulcers. J. Pharm. Sci. and Res, **2009**, 1 (4), 81-87.

44. Ramesh R.P. and Mahesh C.P. Pharmaceutical formulation and development of floating and swellable sustained drug delivery systems: a review. E-Journal of Science and Technology, **2009**, 4 (2), 1-12.

45. Robinson JR, Lee VHL. Controlled drug delivery fundamentals and applications, 2nd edn, Informa Health care, Inc, New York, **2005**, 3-12, 40-43, 56-67.

46. Rowe R.C, Sheskey P.J. and Weller P.J. Handbook of pharmaceutical excipients. 4th edn., Pharmaceutical Press and the American Pharmaceutical Association, London, **2003**, 108, 297, 508, 552, 691.

47. Sable V., Sakarkar S. N. and Pund S. Formulation and evaluation of floating dosage forms an overview. Systematic Reviews In Pharmacy, **2010**, 1(1) ,33-39.

48. Sanjay S.P, Ray S. and Thakur R.S. Formualtion and evaluation of floating drug delivery system containing clarithromycin for helicobacter pylori. Acta Poloniae Pharmaceutica Drug Research, **2006**, 63 (1), 53-61.

49. Satish Singh, Harikumar SL. *In-vitro* and *in-vivo* studies of Celecoxib non effervescent floating microparticulates. Inventi Journals (P) Ltd. Pharm Tech, **2012**; Issue 2, ISSN: 0976-3783.

50. Sauzet C, Claeys B.M, Nicolasc M, Kister J, Piccerelle P. and Prinderrea P. An innovative floating gastro retentive dosage system: Formulation and *In-vitro* evaluation. International Journal of Pharmaceutics, **2009**, 378, 23–29.

51. Shahzad MK, Ubaid M. and Murtaza G, Formulation and Optimization of Celecoxib-Loaded Microspheres Using Response Surface Methodology, Tropical Journal of Pharmaceutical Research October **2012**; 11 (5): 695-702

52. Shishu N, Gupta N. and Aggarwal N. A gastro-retentive floating delivery system for 5-fluorouracil. Asian Journal of Pharmaceutical Sciences, **2007**, 2 (4), 143-149.

53. Shoba Rani R and Hiremath. Text Book of Industrial Pharmacy.1stedn. Black Swan Pulishers Ltd, Chennai, **2008**, 117-128.

54. Shweta A, Javed A, Alka A, Khar R.K. and Sanjula B. Floating Drug Delivery Systems: A Review. AAPS PharmSciTech, **2005**, 6 (3), E372-E390.

55. Thakkar V.T, Shah P.A, Soni T.G, Parmar M.Y, Gohel M.C. and Gandhi T R. Fabrication and evaluation of levofloxacin hemihydrate floating tablet. Research in Pharmaceutical Sciences, **2008**, 3(2), 1-8.

56. Tortora G. and Derrickson B. Principles of anatomy and physiology. 11th edn, John Wiley and Sons Inc; USA, **2003**, 911-913.

57. Venkatesan P., Manavalan R. and Valliappan K. Preparation and Evaluation of Sustained Release Loxoprofen, Journal of Basic and Clinical Pharmacy, **2011**, 159-162.

58. Vishal G.K, Manish A.S, Ritesh R.K, Barhate S.D. and Tupkari S.V. Formulation and evaluation of floating tablets of furosemide. International journal of Pharmaceutical Research and Dosage Form, **2010**, 12(1), 1-9.

59. Yasunori S, Yoshiaki K, Takeuchi H. Physicochemical properties to determine the buoyancy of hollow microspheres prepared by the emulsion solvent diffusion method. Euro. J. Pharm. Biopharma **2003**, 297-304.